RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L100 ANSWER 12 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1998:276325 HCAPLUS
DOCUMENT NUMBER: 129:12200
TITLE: The potential application of cyclo-oxygenase type 2 inhibitors to Alzheimer's disease
AUTHOR(S): Sandson, Thomas A.; Felician, Olivier
CORPORATE SOURCE: Beth Israel Deaconess Med. Cent., Harvard Med. Sch., Boston, MA, 02215, USA
SOURCE: Expert Opinion on Investigational Drugs (1998), 7(4), 519-526
CODEN: EOIDER; ISSN: 1354-3784
PUBLISHER: Ashley Publications
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 58 refs. Dramatic progress has been made in the understanding of the neurogenetics and neurobiol. of **Alzheimer disease** (AD). Inflammatory mechanisms may be involved in the pathophysiol. of AD. Epidemiol. studies have revealed that anti-inflammatory medications reduce the risk of developing AD. Long-term use of conventional anti-inflammatory drugs is assocd. with significant toxicity which limits their potential application in the treatment or prevention of AD. The inhibition of cyclooxygenase type-1 (COX-1) may cause much of this toxicity, while inhibition of COX type-2, which is induced by inflammatory stimuli, may confer the anti-inflammatory effect. COX-2 is also constitutively expressed in brain regions preferentially affected in **Alzheimer disease** and may be directly involved in neuronal cell death. Selective **COX-2 inhibitors** represent a promising class of drugs for the treatment of AD.

REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

(**COX-2**) **inhibitors** in the presence of H. pylori infection are largely derived from animal expts. and indirect clin. evidence. In animal models of H. pylori **gastritis**, **COX-2 inhibitors** suppressed prostaglandin synthesis and aggravated mucosal damage. In the human stomach, COX-1 appears to be the predominant source of prostaglandins despite the fact that COX-2 is upregulated in H. pylori **gastritis**. There are conflicting data on whether H. pylori alters the risk of ulcer in patients receiving **COX-2 inhibitors**. Among patients with H. pylori infection, rofecoxib reduced the risk of complicated gastric but not duodenal ulcers as compared to naproxen. The advantage of rofecoxib over naproxen also disappeared in patients with H. pylori infection and prior upper gastrointestinal events. In contrast, pooled data suggested that H. pylori increases the risk of ulcer in patients receiving nonselective nonsteroidal anti-inflammatory drugs but not in patients receiving celecoxib. In rodent gastric ulcers, COX-2 was upregulated in the granulation tissue and ulcer margin. Inhibition of COX-2 delayed healing of exptl. gastric ulcer. Limited data showed that COX-2 expression was also increased in human gastric ulcer regardless of the H. pylori status. The functional significance of COX-2 in human gastric ulcer is unknown.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:109135 HCAPLUS
DOCUMENT NUMBER: 139:46185
TITLE: Chemoprevention of Helicobacter pylori-associated gastric carcinogenesis in a mouse model; is it possible?
AUTHOR(S): Hahm, Ki Baik; Song, Young Joon; Oh, Tae Young; Lee, Jeong Sang; Surh, Young-Joon; Kim, Young Bae; Yoo, Byung Moo; Kim, Jin Hong; Han, Sang Uk; Nahm, Ki Taik; Kim, Myung-Wook; Kim, Dae Yong; Cho, Sung Won
CORPORATE SOURCE: Genomic Research Center for Gastroenterology, Ajou Helicobacter Research Group, Ajou University School of Medicine, Suwon, S. Korea
SOURCE: Journal of Biochemistry and Molecular Biology (2003), 36(1), 82-94
CODEN: JBMBE5; ISSN: 1225-8687
PUBLISHER: Biochemical Society of the Republic of Korea
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Although debates still exist whether Helicobacter pylori infection is really class I carcinogen or not, H. pylori has been known to provoke precancerous lesions like gastric adenoma and chronic atrophic **gastritis** with intestinal metaplasia as well as gastric cancer. Chronic persistent, uncontrolled gastric inflammations are possible basis for ensuing gastric carcinogenesis and H. pylori infection increased COX-2 expressions, which might be the one of the mechanisms leading to gastric cancer. To know the implication of long-term treatment of antiinflammatory drugs, rebamipide or nimesulide, on H. pylori-assocd. gastric carcinogenesis, we infected C57BL/6 mice with H. pylori, esp. after MNU administration to promote carcinogenesis and the effects of the long-term administration of rebamipide or nimesulide were evaluated. C57BL/6 mice were sacrificed 50 wk after H. pylori infection. Colonization rates of H. pylori, degree of gastric inflammation and other pathol. changes including atrophic **gastritis** and metaplasia, serum levels and mRNA transcripts of various mouse cytokines and chemokines, and

NF-κB binding activities, and finally the presence of gastric adenocarcinoma were compared between H. pylori infected group (HP), and H. pylori infected group administered with long-term rebamipide contg. pellet diets (HPR) or nimesulide mixed pellets (HPN). Gastric mucosal expressions of ICAM-1, HCAM, MMP, and transcriptional regulations of NF-κB binding were all significantly decreased in HPR group than in HP group. Multi-probe RNase protection assay showed the significantly decreased mRNA levels of apoptosis related genes and various cytokines genes like IFN-γ, RANTES, TNF-α, TNFR p75, IL-1β in HPR group. In the expt. designed to provoke gastric cancer through MNU treatment with H. pylori infection, the incidence of gastric carcinoma was not changed between HP and HPR group, but significantly decreased in HPN group, suggesting the chemoprevention of H. pylori-assocd. gastric carcinogenesis by **COX-2 inhibition**. Long-term administration of antiinflammatory drugs should be considered in the treatment of H. pylori since they showed the mol. and biol. advantages with possible chemopreventive effect against H. pylori-assocd. gastric carcinogenesis. If the final concrete proof showing the causal relationship between H. pylori infection and gastric carcinogenesis could be obtained, that will shed new light on chemoprevention of gastric cancer, i.e., that gastric cancer could be prevented through either the eradication of H. pylori or lessening the inflammation provoked by H. pylori infection in high risk group.

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:16663 HCAPLUS
DOCUMENT NUMBER: 136:240946
TITLE: Prevention and treatment of gastrointestinal symptoms and complications due to NSAIDs
AUTHOR(S): McCarthy, Denis M.
CORPORATE SOURCE: VA Medical Center, University of New Mexico, Albuquerque, NM, 87108, USA
SOURCE: Best Practice & Research, Clinical Gastroenterology (2001), 15(5), 755-773
CODEN: BPRCB6
PUBLISHER: Bailliere Tindall
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. The mechanisms by which aspirin(ASA) and non-steroidal anti-inflammatory drugs (NSAIDs) cause gastrointestinal symptoms are poorly understood. They probably arise from several causes, including direct and indirect mucosal injury, exacerbation of underlying peptic ulcer disease or non-ulcer dyspepsia, exacerbation of Helicobacter pylori **gastritis**, and possibly motility disorders. No single form of therapy has been generally successful. Because, in most cases, symptoms abate fairly rapidly with continued treatment, there is little evidence that benefit assocd. with any symptom-directed drug therapy is superior to placebo beyond 4 wk. Exceptions may be the subsets of patients with pre-existing ulcer disease or heartburn, exacerbated by the NSAID therapy, who usually benefit from acid-suppressive drug treatment. Different NSAIDs vary in the frequency with which their use leads to gastrointestinal(GI) complications such as hemorrhage, perforation, obstruction, or the symptomatic ulcers from which about 40% of the complications arise. Most gastroduodenal ulcers heal over time, albeit more slowly, with conventional doses of any of the available anti-ulcer

drugs. Maintenance therapy may be needed in many patients who continue NSAID therapy. Anti-ulcer drugs have not, thus far, been shown to be more effective than placebo in preventing ulcer complications or their recurrence. The use of COX-2-selective inhibitors appears, in outcome studies, to reduce gastrointestinal bleeding, including bleeding from ulcers, but it is not established that the ulcers protected were caused by NSAIDs, as distinct from ulcers exacerbating or recurring from antecedent peptic ulcer disease. To-date, perforation or obstruction have not been shown to be affected by selective **COX-2 inhibitor** drugs. If the major problem giving rise to severe NSAID complications is pre-existing peptic ulcer disease, it may yet emerge that the most effective approach will be the use of proton pump inhibitor drugs, for the duration of NSAID therapy, in a small subset of high-risk patients. Most other low-risk patients may not need any special care. Co-morbid conditions have a major impact on outcome of NSAID therapy. Morbidity or even death attributable solely to NSAIDs is probably small in normal patients, and requires little in the way of prophylaxis.

REFERENCE COUNT: 92 THERE ARE 92 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:820286 HCAPLUS
DOCUMENT NUMBER: 136:367108
TITLE: Role of cyclooxygenase isoforms in gastric mucosal defense
AUTHOR(S): Peskar, B. M.
CORPORATE SOURCE: Department of Experimental Clinical Medicine, University of Bochum, Bochum, D-44780, Germany
SOURCE: Journal of Physiology (Paris) (2001), 95(1-6), 3-9
CODEN: JHYSEM; ISSN: 0928-4257
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. A complex system of interacting mediators exists in the gastric mucosa to strengthen its resistance against injury. In this system prostaglandins play an important role. Prostaglandin biosynthesis is catalyzed by the enzyme cyclooxygenase (COX), which exists in 2 isoforms, COX-1 and COX-2. Initially the concept was developed that COX-1 functions as housekeeping enzyme, whereas COX-2 yields prostaglandins involved in pathophysiol. reactions such as inflammation. In the gastrointestinal tract, the maintenance of mucosal integrity was attributed exclusively to COX-1 without a contribution of COX-2 and ulcerogenic effects of non-steroidal anti-inflammatory drugs (NSAIDs) were believed to be the consequence of inhibition of COX-1. Recent findings, however, indicate that both COX-1 and COX-2 either alone or in concert contribute to gastric mucosal defense. Thus, in normal rat gastric mucosa specific inhibition of COX-1 does not elicit mucosal lesions despite near-maximal suppression of gastric prostaglandin formation. When a selective **COX-2 inhibitor** which is not ulcerogenic when given alone is added to the COX-1 inhibitor, severe gastric damage develops. In contrast to normal gastric mucosa which requires simultaneous inhibition of COX-1 and COX-2 for breakdown of mucosal resistance, in the acid-challenged rat stomach inhibition of COX-1 alone results in dose-dependent injury which is further increased by addnl. inhibition of COX-2 enzyme activity or prevention of acid-induced up-regulation of COX-2 expression by dexamethasone. **COX-2 inhibitors** do not damage the normal or acid-challenged gastric mucosa when given alone. However, when nitric oxide formation is suppressed or afferent nerves are defunctionalized,

specific inhibition of COX-2 induces severe gastric damage. Ischemia-reperfusion of the gastric artery is assocd. with up-regulation of COX-2 but not COX-1 mRNA. **COX-2 inhibitors** or dexamethasone augment ischemia-reperfusion-induced gastric damage up to 4-fold, an effect abolished by concurrent administration of 16,16-dimethyl-PGE2. Selective inhibition of COX-1 is less effective. Furthermore, **COX-2 inhibitors** antagonize the protective effect of a mild irritant or intragastric peptone perfusion in the rat stomach, whereas the protection induced by chronic administration of endotoxin is mediated by COX-1. Finally, an important function of COX-2 is the acceleration of ulcer healing. COX-2 is up-regulated in chronic gastric ulcers and inhibitors of COX-2 impair the healing of ulcers to the same extent as non-selective NSAIDs. Taken together, these observations show that both COX isoenzymes are essential factors in mucosal defense with specific contributions in various physiol. and pathophysiol. situations.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> d his

     (FILE 'HOME' ENTERED AT 10:48:57 ON 15 JUN 2004)

     FILE 'REGISTRY' ENTERED AT 10:49:17 ON 15 JUN 2004

     FILE 'HCAPLUS' ENTERED AT 10:49:39 ON 15 JUN 2004
L1          2615 S COX-2 () INHIBIT?
L2          1536 S L1 AND INFLAMMAT?
L3           434 S L2 AND REVIEW/DT
L4            22 S L1 AND INFLAMMAT? () DISORDER?
L5             6 S L4 AND REVIEW/DT
L6            41 S L1 AND ULCERAT? () COLIT?
L7             1 S L6 AND REVIEW/DT
L8            72 S L1 AND ASTHMA?
L9            12 S L8 AND REVIEW/DT
L10           56 S L1 AND CROHN?
L11            1 S L10 AND REVIEW/DT
L12           33 S L1 AND GASTRIT?
L13            5 S L12 AND REVIEW/DT

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        686545 DISEASE
        191032 DISEASES
        776485 DISEASE
                  (DISEASE OR DISEASES)
             0 VASCUL (W) DISEASE
L14          0 L1 AND VASCUL (W) DISEASE

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        781585 DISEASE?
          5957 VASCUL? (W) DISEASE?
L15          9 L1 AND VASCUL? (W) DISEASE?

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       1734424 REVIEW/DT
L16          3 L15 AND REVIEW/DT

=> d l16, ibib abs, 1-3
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L16 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:298084 HCAPLUS
DOCUMENT NUMBER: 139:20205
TITLE: Cyclooxygenase isoforms and atherosclerosis
AUTHOR(S): Belton, Orina; Fitzgerald, Desmond J.
CORPORATE SOURCE: Dep. Clinical Pharmacology, Royal College Surgeons in Ireland, Dublin, Ire.
SOURCE: Expert Reviews in Molecular Medicine (2003), 5, No pp. given
CODEN: ERMMFS; ISSN: 1462-3994
URL: http://www.expertreviews.org/03005842a.pdf
PUBLISHER: Cambridge University Press
DOCUMENT TYPE: Journal; **General Review**; (online computer file)
LANGUAGE: English

AB A review. Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of arthritis and pain. However, their long-term use is limited by gastrointestinal (GI) side effects such as gastric ulcers. NSAIDs act by inhibiting an enzyme called cyclooxygenase. Cyclooxygenase (COX) catalyzes the generation of prostaglandins from arachidonic acid. Two isoforms of the enzyme exist - COX-1 and COX-2 - both of which are targets for NSAIDs. Although they are assocd. with GI toxicity, NSAIDs have important antithrombotic and anti-inflammatory effects. The GI injury has been attributed to COX-1 inhibition and the anti-inflammatory effects to **COX-2 inhibition**. As COX-2 is traditionally viewed as an inducible enzyme, selective inhibition of COX-2 by 'coxibs' (selective **COX-2 inhibitors**) has been employed to achieve anti-inflammatory and analgesic effects without GI side effects. However, recently there have been suggestions that chronic administration of coxibs might increase the risk of cardiovascular events, such as atherosclerosis, compared with traditional NSAIDs. In **vascular disease**, there is increased expression of both COX-1 and COX-2, resulting in enhanced prostaglandin generation. The specific role of COX-1 and COX-2 in vascular regulation is still unknown but such knowledge is essential for the effective use of coxibs. Although more evidence is pointing to selective COX-1 inhibition as a therapeutic measure in inflammatory atherosclerosis, there are some studies that suggest that inhibition of COX-2 might have a potential benefit on atherosclerosis.

REFERENCE COUNT: 136 THERE ARE 136 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:16666 HCAPLUS
DOCUMENT NUMBER: 136:240948
TITLE: COX-1 and **COX-2 inhibitors**
AUTHOR(S): Hawkey, C. J.
CORPORATE SOURCE: Division of Gastroenterology, University Hospital Nottingham, Nottingham, NG7 2UH, UK
SOURCE: Best Practice & Research, Clinical Gastroenterology (2001), 15(5), 801-820
CODEN: BPRCB6
PUBLISHER: Bailliere Tindall
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. By inhibiting prostaglandin synthesis, non-steroidal

anti-inflammatory drugs (NSAIDs) cause mucosal damage, ulceration and ulcer complication throughout the gastrointestinal tract. The recognition that there are two cyclo-oxygenase enzymes, one predominating at sites of inflammation (COX-2) and one constitutively expressed in the gastrointestinal tract (COX-1), has led to the important therapeutic development of **COX-2 inhibitors**. COX-2 is phylogenetically more primitive that COX-1 and, while very similar, has crit. differences, particularly the existence of a small pocket half way down the active enzyme site. A no. of drugs achieve selectivity by binding to this pocket, including presumptively rofecoxib and celecoxib. Others, such as meloxicam, may inhibit COX-2 by different mechanisms. Truly selective **COX-2 inhibitors** have been shown to have no effect on gastric mucosal prostaglandin synthesis, to cause no acute injury, and no chronic ulceration compared to placebo. Rofecoxib has, in a prospective systematic evaluation involving 8076 patients, been shown to reduce clin. significant ulcers, ulcer complications and gastrointestinal bleeding significantly compared to naproxen. Outcomes data for celecoxib have also been published although differences from the combined comparator agents (diclofenac and ibuprofen) did not reach statistical significance. Use of aspirin in the class study has shown that the benefits of **COX-2 inhibitors** may be reduced by aspirin use. The VIGOR study has raised the possibility that some NSAIDs, particularly naproxen, may protect against **vascular disease** compared to **COX-2 inhibitors** (or placebo).

REFERENCE COUNT: 117 THERE ARE 117 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:289726 HCAPLUS
DOCUMENT NUMBER: 135:220416
TITLE: Cyclooxygenase products and atherothrombosis
AUTHOR(S): FitzGerald, Garret A.; Austin, Sandra; Egan, Karine; Cheng, Yan; Pratico, Domenico
CORPORATE SOURCE: Center for Experimental Therapeutics, University of Pennsylvania, Philadelphia, PA, USA
SOURCE: Annals of Medicine (Helsinki, Finland) (2000), 32(Suppl. 1), 21-26
CODEN: ANMDEU; ISSN: 0785-3890
PUBLISHER: Royal Society of Medicine Press Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 51 refs. The advent of selective inhibitors of the cyclooxygenase (COX)-2 enzyme has afforded the opportunity to reduce the incidence of gastrointestinal complications of traditional nonsteroidal anti-inflammatory drugs (NSAIDs). The widespread use of these drugs has increased interest in their role in the cardiovascular system. Although deletion of the prostacyclin receptor accelerates atherogenesis in the mouse, retention of one copy of the receptor is atheroprotective. This is consistent with the failure of biochem. defined, selective doses of a **COX-2 inhibitor** to accelerate atherogenesis in the mouse, despite suppressing prostacyclin biosynthesis by roughly 60%. Inhibition of both COX isoenzymes, by contrast, markedly retards atherogenesis. Consistent with these observations, antagonism of the thromboxane receptor retards atherogenesis and diminishes the proliferative response to vascular injury in the mouse. Even partial suppression of prostacyclin (without coincident inhibition of platelet COX-1-dependent thromboxane formation) by **COX-2 inhibitors** may be undesirable in acute vascular occlusive syndromes. However, these drugs are unlikely to accelerate progression of

the underlying **vascular disease**. By contrast, the effects of thromboxane receptor antagonists, aspirin, and even traditional NSAIDs on atherosclerotic plaque progression merit further evaluation in humans.
REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> s l1 and allergic () rhinit?
         27824 ALLERGIC
            67 ALLERGICS
         27844 ALLERGIC
                 (ALLERGIC OR ALLERGICS)
          4247 RHINIT?
          2641 ALLERGIC (W) RHINIT?
L17         15 L1 AND ALLERGIC (W) RHINIT?

=> s l17 and review/dt
       1734424 REVIEW/DT
L18          0 L17 AND REVIEW/DT

=> s l1 and aller?
         56496 ALLER?
L19         71 L1 AND ALLER?

=> s l19 and review/dt
       1734424 REVIEW/DT
L20          4 L19 AND REVIEW/DT

=> d l20, ibib abs, 1-4

L20  ANSWER 1 OF 4  HCAPLUS  COPYRIGHT 2004 ACS on STN
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Full Text | Citing References

ACCESSION NUMBER: 2003:370812 HCAPLUS
DOCUMENT NUMBER: 139:94634
TITLE: Anaphylactic and anaphylactoid reactions to aspirin and other NSAIDs
AUTHOR(S): Berkes, Eva A.
CORPORATE SOURCE: Sarasota Allergy and Asthma Specialty Clinic, Sarasota, FL, 34233, USA
SOURCE: Clinical Reviews in Allergy & Immunology (2003), 24(2), 137-147
CODEN: CRAIF2; ISSN: 1080-0549
PUBLISHER: Humana Press Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Aspirin and non-steroidal antiinflammatory drugs (NSAIDs) may cause anaphylactic or anaphylactoid reactions. Constitutively-expressed cyclooxygenase (COX-1) inhibition is likely to be responsible for the cross-reactions and side effects assocd. with these drugs, as well as the anaphylactoid reactions sometimes seen in aspirin-sensitive respiratory disease. Though anaphylactic and anaphylactoid reactions may be clin. indistinguishable, they involve different mechanisms. Anaphylactic reactions are due to immediate hypersensitivity involving crosslinking of drug-specific IgE. Regardless of COX selectivity pattern, NSAIDs may function as haptens capable of inducing **allergic** sensitization. Unlike anaphylaxis, anaphylactoid reactions are most likely related to inhibition of COX-1 by NSAIDS. Thus, an anaphylactoid reaction caused by a particular COX-1 inhibiting NSAID will occur with a chem. unrelated NSAID which also inhibits COX-1 enzymes. Selective **COX-2 inhibitors**

appear to be safe in patients with a history of NSAID-related anaphylactoid reactions but can function as haptens, with resulting sensitization and anaphylaxis upon next exposure. This article will discuss the mechanisms, prevalence and population-based studies of anaphylactic and anaphylactoid reactions caused by aspirin and NSAIDs. The evaluation and management of patients suspected of having experienced an anaphylactic or anaphylactoid reaction to aspirin or other NSAIDs will also be reviewed.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:136698 HCAPLUS
DOCUMENT NUMBER: 136:395185
TITLE: Non steroidal anti-inflammatory and anti-**allergy** agents
AUTHOR(S): Kontogiorgis, C. A.; Hadjipavlou-Litina, D. J.
CORPORATE SOURCE: Department of Pharmaceutical Chemistry, School of Pharmacy, Aristotelian University of Thessaloniki, Thessaloniki, 54006, Greece
SOURCE: Current Medicinal Chemistry (2002), 9(1), 89-98
CODEN: CMCHE7; ISSN: 0929-8673
PUBLISHER: Bentham Science Publishers
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Non steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used for inflammation therapy. The major drawback in using the NSAIDs is in their tendency to cause gastrointestinal toxicity. Since the roles of arachidonic acid (A.A) metabolites, as leukotrienes (Lts), prostaglandins (PGs) and thromboxanes (TXA2) as mediators of the inflammatory reaction were clarified, much effort has been made to develop inhibitors of the prodn. of these chem. mediators as anti-inflammatory agents. These mediators also play important roles in some inflammatory or **allergic** diseases, acting either alone or in combination and inhibitors of 5-lipoxygenase (5-LOX) and/or cyclooxygenase isoforms 1,2 (COX-1,2) may be useful for the treatment of asthma, psoriasis and rheumatoid arthritis. Leukotrienes, the products of 5-LOX metab. have been assocd. with immediate hypersensitivity reactions, anaphylaxis and asthma. In addn., active oxygen species (AOS) including superoxide anion (O2-), hydrogen peroxide, hydroxyl radical and ferric radical, mediate cell damage in a variety of pathophysiol. conditions and are responsible for oxidative injury of enzymes, lipid membranes and DNA in living cells and tissues. Prostaglandins and leukotrienes in the arachidonate pathway linked with lipid peroxidn. may amplify the oxidative damage. Nitric oxide (NO) plays also a role as an effector in inflammation, since PG and NO thought to be important in maintaining mucosal integrity. Dual or selective inhibitors, specific receptor antagonists, AOS scavengers, and NO donors have been under development for therapeutic application. Several classes of inhibitors have been identified and at least 12 major chem. series are known to affect PGs prodn. directly. In this review, we account on our research work concerning NSAIDs combined with a ref. of the recent literature.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:349750 HCAPLUS
DOCUMENT NUMBER: 135:220476
TITLE: Nonsteroidal anti-inflammatory drugs in systemic lupus erythematosus
AUTHOR(S): Ostensen, M.; Villiger, P. M.
CORPORATE SOURCE: Department of Rheumatology, Clinical Immunology and Allergy, University Hospital of Berne, Bern, Switz.
SOURCE: Lupus (2001), 10(3), 135-139
CODEN: LUPUES; ISSN: 0961-2033
PUBLISHER: Arnold, Hodder Headline
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 34 refs. Up to 80% of patients with systemic lupus erythematosus (SLE) are treated with nonsteroidal anti-inflammatory drugs (NSAID) for musculoskeletal symptoms, serositis and headache. This survey reviews the literature on non-selective and selective inhibitors of cyclooxygenases with an emphasis on the efficacy and safety profile reported in SLE patients. No lupus-specific data on gastro-intestinal side effects of NSAID exist. Both non-selective Cox-inhibitors and selective **Cox-2 inhibitors** induce renal side effects including sodium retention and redn. of the glomerular filtration rate. Lupus nephritis is a risk factor for NSAID-induced acute renal failure, but not for rare idiosyncratic toxic renal reactions to NSAID. In refractory nephrotic syndrome, NSAID have been used successfully. Cutaneous and **allergic** reactions to NSAID are increased in SLE patients as well as hepatotoxic effects, particularly with high dose aspirin. Whereas a variety of central nervous system side effects of NSAID are probably no more common in SLE patients than in others, aseptic meningitis has been reported more frequently. Ovulation and pregnancy can be adversely affected by Cox-inhibitors. The antiplatelet effect of aspirin and non-selective Cox-inhibitors has a therapeutic potential in patients with the antiphospholipid syndrome (APS). In summary, treatment of SLE with NSAID requires awareness for the increased frequency of some side effects and close monitoring of toxicity.
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN
Full Text | Citing References

ACCESSION NUMBER: 2000:754174 HCAPLUS
DOCUMENT NUMBER: 134:320365
TITLE: Nonsteroidal anti-inflammatory drugs in systemic lupus erythematosus
AUTHOR(S): Ostensen, M.; Villiger, P. M.
CORPORATE SOURCE: Department of Rheumatology, Clinical Immunology and Allergy, University Hospital of Berne, Bern, CH-3010, Switz.
SOURCE: Lupus (2000), 9(8), 566-572
CODEN: LUPUES; ISSN: 0961-2033
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 60 refs. Up to 80% of patients with systemic lupus erythematosus (SLE) are treated with nonsteroidal antiinflammatory drugs (NSAID) for musculoskeletal symptoms, serositis and headache. This survey reviews the literature on non-selective and selective inhibitors of cyclooxygenases, with an emphasis on the efficacy and safety profile reported in SLE patients. No lupus-specific data on gastro-intestinal side effects of NSAID exist. Both non-selective Cox inhibitors and

selective **Cox-2 inhibitors** induce renal side effects, including sodium retention and redn. of the glomerular filtration rate. Lupus nephritis is a risk factor for NSAID-induced acute renal failure, but not for rare idiosyncratic toxic renal reactions to NSAID. In refractory nephrotic syndrome, NSAID have been used successfully. Cutaneous and **allergic** reactions to NSAID are increased in SLE patients as well as hepatotoxic effects, particularly with high dose aspirin. Whereas a variety of central nervous system side effects of NSAID are probably no more common in SLE patients than others, aseptic meningitis has been reported more frequently. Ovulation and pregnancy can be adversely affected by Cox inhibitors. The antiplatelet effect of aspirin and non-selective Cox inhibitors has a therapeutic potential in patients with antiphospholipid syndrome (APS). In summary, treatment of SLE with NSAID requires awareness for the increased frequency of some side effects and close monitoring of toxicity.

REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> s l1 and irrit? () bowel? () syndrome?
         28978 IRRIT?
         11625 BOWEL?
         95996 SYNDROME?
          1374 IRRIT? (W) BOWEL? (W) SYNDROME?
L21          9 L1 AND IRRIT? (W) BOWEL? (W) SYNDROME?

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L22          0 L21 AND REVIEW/DT

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         11625 BOWEL?
          1394 IRRIT? (W) BOWEL?
L23          9 L1 AND IRRIT? (W) BOWEL?

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           160 MIGRAINES
          4328 MIGRAINE
                 (MIGRAINE OR MIGRAINES)
L24         31 L1 AND MIGRAINE

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L25          2 L24 AND REVIEW/DT

=> d l25, ibib abs, 1-2

L25  ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2004 ACS on STN
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Full Text | Citing References

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ACCESSION NUMBER:        2001:554480  HCAPLUS
DOCUMENT NUMBER:         135:326832
TITLE:                   The clinical developments and future of the COX-2
                         inhibitor drugs
AUTHOR(S):               Goldstein, Jerome
CORPORATE SOURCE:        San Francisco Clinical Research Center, San Francisco,
                         CA, 94109, USA
SOURCE:                  Inflammopharmacology (2001), 9(1-2), 91-99
```

CODEN: IAOAES; ISSN: 0925-4692
PUBLISHER: VSP BV
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review, with refs. A new era of analgesia began with the discovery of aspirin in 1899. Since that time, many newer NSAIDs (non-steroid anti-inflammatory drugs) have been discovered and utilized in clin. practice. The mechanism of anti-inflammatory action of NSAIDs is believed to result from inhibition of the enzyme cyclooxygenase (COX), discovered in the 1970s. This enzyme represents the key rate-limiting step in the prodn. of prostaglandins (PGs) from arachidonic acid. Since PGs are essential for normal gastrointestinal, renal, and platelet function, as well as mediating the inflammatory process, inhibition of cyclooxygenase has both beneficial and deleterious effects. The beneficial effect, obviously, is inhibition of the inflammatory process, while the harmful effects comprise an increased incidence of upper gastrointestinal toxicity (ulceration, perforation, and bleeding) as well as possible renal and platelet dysfunction. In the late 1980s, it was discovered that two isoforms of cyclooxygenase existed (COX-1 and COX-2). COX-1 represents a constitutive form that is expressed in most tissues. In contrast, COX-2 is induced at sites of inflammation and also occurs under normal circumstances in the brain and renal tissues. Since COX-2 levels increase dramatically during acute and chronic inflammation, it was hypothesized that the **COX-2 inhibitors** might offer significant anti-inflammatory qualities with reduced toxicity and may have utility in central nervous system mediated conditions other than peripheral pain, including dementias such as Alzheimer's disease and headache, specifically, **migraine** headache.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:263605 HCAPLUS
DOCUMENT NUMBER: 135:70473
TITLE: Novel serotonergic and non-serotonergic **migraine** headache therapies
AUTHOR(S): Slassi, Abdelmalik; Isaac, Methvin; Arora, Jalaj
CORPORATE SOURCE: Discovery Chemistry Department, NPS Allelix Corp., Mississauga, ON, L4V 1V7, Can.
SOURCE: Expert Opinion on Therapeutic Patents (2001), 11(4), 625-649
CODEN: EOTPEG; ISSN: 1354-3776
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 196 refs. In the last four years discovery of pharmacotherapeutic treatments for **migraine** headaches has received much attention. Since the patent literature was last reviewed in 1997 [1], advances have been made in the understanding of mechanism and pathophysiol. of **migraine**. Introduction of sumatriptan to the market has led to acceleration in research efforts towards finding safe and effective treatments for **migraine**. The importance of this field is evidenced by the no. of compds. in clin. trials and by the no. of patents filed in recent years. For example, besides sumatriptan, a second generation of three new drugs (naratriptan [2], zolmitriptan [3] and rizatriptan [4]) has entered the marketplace and few others are presently in clin. evaluation. In addn., classical drug design has yielded highly potent and selective ligands to target relevant receptor subtypes in **migraine** treatment. This article highlights and reviews the research

advances published in patent literature between Jan. 1997 through Nov. 2000. The article is supplemented with selected refs. on design and development of novel agents with which to treat **migraine** and to study its mechanism and pathophysiol. Emphasis is made on serotonergic agents, namely serotonin (5-hydroxytryptamine, 5-HT) receptor subtype (5-HT1D, 5-HT1F and 5-HT5) agonists, drug combinations (e.g., 5-HT1D agonists with **COX-2 inhibitors** or NSAIDs), tachykinin receptor (NK1) antagonists and GABAergic agents. Also included are patents describing chem. entities that may be effective in **migraine** therapy based on their pharmacol. actions as anticonvulsants, LTD4 receptor blocker agents and thromboxane inhibitors. By no means has any attempt been made to exhaustively review the literature; but rather, primary refs. along with citations to latest literature reviews have been included in each section.

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=> d his

     (FILE 'HOME' ENTERED AT 10:48:57 ON 15 JUN 2004)

     FILE 'REGISTRY' ENTERED AT 10:49:17 ON 15 JUN 2004

     FILE 'HCAPLUS' ENTERED AT 10:49:39 ON 15 JUN 2004
L1          2615 S COX-2 () INHIBIT?
L2          1536 S L1 AND INFLAMMAT?
L3           434 S L2 AND REVIEW/DT
L4            22 S L1 AND INFLAMMAT? () DISORDER?
L5             6 S L4 AND REVIEW/DT
L6            41 S L1 AND ULCERAT? () COLIT?
L7             1 S L6 AND REVIEW/DT
L8            72 S L1 AND ASTHMA?
L9            12 S L8 AND REVIEW/DT
L10           56 S L1 AND CROHN?
L11            1 S L10 AND REVIEW/DT
L12           33 S L1 AND GASTRIT?
L13            5 S L12 AND REVIEW/DT
L14            0 S L1 AND VASCUL () DISEASE
L15            9 S L1 AND VASCUL? () DISEASE?
L16            3 S L15 AND REVIEW/DT
L17           15 S L1 AND ALLERGIC () RHINIT?
L18            0 S L17 AND REVIEW/DT
L19           71 S L1 AND ALLER?
L20            4 S L19 AND REVIEW/DT
L21            9 S L1 AND IRRIT? () BOWEL? () SYNDROME?
L22            0 S L21 AND REVIEW/DT
L23            9 S L1 AND IRRIT? () BOWEL?
L24           31 S L1 AND MIGRAINE
L25            2 S L24 AND REVIEW/DT

=> s l1 and periarterits? () nodos?
             0 PERIARTERITS?
          2546 NODOS?
             0 PERIARTERITS? (W) NODOS?
L26          0 L1 AND PERIARTERITS? (W) NODOS?

=> s l1 and periart?
          1188 PERIART?
L27         14 L1 AND PERIART?

=> s l27 and review/dt
       1734424 REVIEW/DT
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L28 2 L27 AND REVIEW/DT

=> d l28, ibib abs, 1-2

L28 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:988882 HCAPLUS
DOCUMENT NUMBER: 140:349806
TITLE: Paracetamol in the treatment of osteoarthritis pain
AUTHOR(S): Brandt, Kenneth
CORPORATE SOURCE: Departements de Rhumatologie et de Chirurgie Orthopedique, Faculte de Medecine, Universite d'Indiana et Centre pluridisciplinaire des maladies rhumatismales et osteoarticulaires de l'Universite d'Indiana, Etats-Unis, USA
SOURCE: Drugs (2003), 63(Spec. Issue), 23-41
CODEN: DRUGAY; ISSN: 0012-6667
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: French

AB A review. Osteoarthritis (OA) is the most common joint disease and OA of the knee, in particular, is the major cause of chronic disability among people >65 yr. Because nonsteroidal anti-inflammatory drugs (NSAIDs) improve symptoms in many patients with OA, it is widely considered that OA pain is due to synovial inflammation. However, OA pain may arise also from subchondral bone, the joint capsule, ligaments, tendons, entheses and **periarticular** muscle spasm. In many patients, the relief of OA pain and overall satisfaction with therapy may be as great with paracetamol (acetaminophen [APAP]) as with an NSAID. Cyclo-oxygenase (COX)-1-sparing NSAIDs (coxibs) are no more effective in the treatment of OA pain than non-selective NSAIDs and, although they may significantly decrease the risk of serious adverse effects related to gastrointestinal ulcers (GI) and ulcer complications, their gastroprotective effect may be reduced by concomitant administration of low-dose aspirin. Also, they may increase the risk of myocardial infarction in predisposed individuals. Because coxibs do not inhibit platelet aggregation, if prophylaxis against thromboembolic disease is required in patients being treated with a selective **COX-2 inhibitor**, low-dose aspirin should be used in conjunction with the coxib. Furthermore, nonselective NSAIDs and coxibs may have adverse effects on the kidney, fracture healing and salt and water homeostasis. This paper discusses the relative positioning of APAP, NSAIDs and coxibs in the management of OA, on the basis of considerations of tolerability, efficacy and costs.

REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L28 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:921953 HCAPLUS
DOCUMENT NUMBER: 138:49176
TITLE: Meloxicam (Mobic): a review of its pharmacological and clinical profile
AUTHOR(S): Ogino, Keiko; Saito, Kazushige; Osugi, Takeshi; Satoh, Hisashi
CORPORATE SOURCE: Dep. Pharmacol. Kawanishi Pharma Res. Inst., Nippon Boehringer Ingelheim, Co., Ltd., Kawanishi, 666-0193, Japan
SOURCE: Nippon Yakurigaku Zasshi (2002), 120(6), 391-397

CODEN: NYKZAU; ISSN: 0015-5691
PUBLISHER: Nippon Yakuri Gakkai
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: Japanese
AB A review. Meloxicam (Mobic) is a new nonsteroidal anti-inflammatory drug (NSAID) derived from enolic acid, exhibiting selectivity for cyclooxygenase (COX)-2 over COX-1. Meloxicam has shown potent anti-inflammatory and analgesic activity together with low gastrointestinal toxicity in animal models. It is a potent inhibitor not only of acute exudation in adjuvant arthritis in the rat, but also of bone and cartilage destruction. The therapeutic range of meloxicam in the rat, with regard to inhibition of adjuvant arthritis, was several times greater than that of other NSAIDs. Meloxicam in therapeutic doses was found to have no effect on bleeding time or platelet aggregation in healthy volunteers. In clin. studies, meloxicam has shown reliable efficacy against rheumatoid arthritis, osteoarthritis, lumbago (low back pain), scapulohumeral **periarthritis**, and neck-shoulder-arm syndrome with low gastrointestinal toxicity.

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=> s l1 and thyroidits?
             0 THYROIDITS?
L29          0 L1 AND THYROIDITS?

=> s l1 and thyroid?
         75461 THYROID?
L30         27 L1 AND THYROID?

=> s l30 and review/dt
       1734424 REVIEW/DT
L31          0 L30 AND REVIEW/DT

=> s l1 and aplastic? () anemia?
          1777 APLASTIC?
         31974 ANEMIA?
          1336 APLASTIC? (W) ANEMIA?
L32          0 L1 AND APLASTIC? (W) ANEMIA?

=> s l1 and aplast?
          1818 APLAST?
L33          1 L1 AND APLAST?

=> s l33 and review/dt
       1734424 REVIEW/DT
L34          0 L33 AND REVIEW/DT

=> s l1 and hodgin? () disease?
            40 HODGIN?
        781585 DISEASE?
             2 HODGIN? (W) DISEASE?
L35          0 L1 AND HODGIN? (W) DISEASE?

=> s l1 and hodgkin? () disease?
          7841 HODGKIN?
        781585 DISEASE?
           845 HODGKIN? (W) DISEASE?
L36          0 L1 AND HODGKIN? (W) DISEASE?

=> s l1 and hodgkin?
          7841 HODGKIN?
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L37           6 L1 AND HODGKIN?

=> s l37 and review/dt
       1734424 REVIEW/DT
L38           0 L37 AND REVIEW/DT

=> s l37 and slerodom?
              0 SLERODOM?
L39           0 L37 AND SLERODOM?

=> s l1 and sclerodom?
              1 SCLERODOM?
L40           0 L1 AND SCLERODOM?

=> s l1 and sclero?
          29630 SCLERO?
L41          59 L1 AND SCLERO?

=> s l41 and review/dt
       1734424 REVIEW/DT
L42           1 L41 AND REVIEW/DT

=> d l42, ibib abs, 1

L42  ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2004 ACS on STN
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Full Text | Citing References

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ACCESSION NUMBER:         2002:46056  HCAPLUS
DOCUMENT NUMBER:          137:3852
TITLE:                    COX-2 and ALS
AUTHOR(S):                McGeer, Patrick L.
CORPORATE SOURCE:         Kinsmen Laboratory of Neurological Research,
                          University of British Columbia, Vancouver, BC, Can.
SOURCE:                   Amyotrophic Lateral Sclerosis and Other Motor Neuron
                          Disorders (2001), 2(3), 121-122
                          CODEN: ALSCFA; ISSN: 1466-0822
PUBLISHER:                Martin Dunitz Ltd.
DOCUMENT TYPE:            Journal; General Review
LANGUAGE:                 English
AB    An editorial review on the role of cyclooxygenase 2 (COX-2) in amyotrophic
      lateral sclerosis (ALS) and the use of COX-2 inhibitors in
      treatment.  A comparison between ALS and Alzheimer's disease (AD) showed
      that COX-2 mRNA levels in ALS spinal cord were 7.9-fold higher than in
      control spinal cords, while there was only a 2.6-fold increase in AD
      hippocampus compared with control hippocampus.  These findings indicate a
      more robust neuroinflammatory reaction in ALS than in AD.
REFERENCE COUNT:          11    THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT


=> s l1 and diabete?
          89654 DIABETE?
L43          59 L1 AND DIABETE?

=> s l43 and review/dt
       1734424 REVIEW/DT
L44           4 L43 AND REVIEW/DT

=> d l44, ibib abs, 1-4
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L44 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2004:138440 HCAPLUS
DOCUMENT NUMBER: 140:318862
TITLE: Cyclooxygenases, the Kidney, and Hypertension
AUTHOR(S): Cheng, Hui-Fang; Harris, Raymond C.
CORPORATE SOURCE: Departments of Medicine, Division of Nephrology, Vanderbilt University School of Medicine, Nashville, TN, USA
SOURCE: Hypertension (2004), 43(3), 525-530
CODEN: HPRTDN; ISSN: 0194-911X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Selective cyclooxygenase (**COX**)-**2 inhibitors** that are in widespread clin. use were developed to avoid side effects of conventional NSAIDs, including gastrointestinal and renal toxicity. However, COX-2 is constitutively expressed in the kidney and is highly regulated in response to alterations in intravascular vol. COX-2 metabolites have been implicated in maintenance of renal blood flow, mediation of renin release, and regulation of sodium excretion. **COX-2 inhibition** may transiently decrease urine sodium excretion in some subjects and induce mild to moderate elevation of blood pressure. Furthermore, in conditions of relative intravascular vol. depletion and/or renal hypoperfusion, interference with COX-2 activity can have deleterious effects on maintenance of renal blood flow and glomerular filtration rate. In addn. to physiol. regulation of COX-2 expression in the kidney, increased renal cortical COX-2 expression is seen in exptl. models assocd. with altered renal hemodynamics and progressive renal injury (decreased renal mass, poorly controlled **diabetes**), and long-term treatment with selective **COX-2 inhibitors** ameliorates functional and structural renal damage in these conditions.

REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:799688 HCAPLUS
DOCUMENT NUMBER: 139:378806
TITLE: The importance of diabetic nephropathy in current nephrological practice
AUTHOR(S): Locatelli, Francesco; Canaud, Bernard; Eckardt, Kai-Uwe; Stenvinkel, Peter; Wanner, Christoph; Zoccali, Carmine
CORPORATE SOURCE: Department of Nephrology and Dialysis, Azienda Ospedale di Lecco, Ospedale A. Manzoni, Lecco, 23900, Italy
SOURCE: Nephrology, Dialysis, Transplantation (2003), 18(9), 1716-1725
CODEN: NDTREA; ISSN: 0931-0509
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Diabetic nephropathy has become the major cause of end-stage renal disease (ESRD) in the western world and is forecast to become the most frequent cause of ESRD in the African continent and in developing countries in other areas. A discussion to achieve a consensus on key points relating to diabetic nephropathy. Given the catastrophic

consequences of **diabetes** not only for renal function but also for the cardiovascular system, major efforts should be aimed at prevention. The cornerstone of primary prevention (development of microalbuminuria) is a tight control of blood pressure and blood glucose. Although ACE inhibitors have proved effective in preventing the development of microalbuminuria in normotensive patients, this is not the case, in comparison with other classes of antihypertensive drugs, in those who are hypertensive but normoalbuminuric. Secondary prevention (transition to overt nephropathy) and tertiary prevention (progression of established nephropathy to ESRD) benefit from the use of inhibitors of the renin-angiotensin system, while the role of tight glycemic control is more controversial at these stages. Therapeutic lifestyle changes are also important. They should include body wt. control combined with regular phys. exercise, cessation of smoking and reduced salt intake. The pathogenesis of diabetic nephropathy and its assocn. with hypertension, accelerating renal damage, is complex. It involves genetic factors, altered renal Na handling with Na retention, metabolic disturbances and oxidative stress with the formation of advanced-glycation end products (AGEs) and reactive oxygen species. Although the awareness of the importance of normalizing blood pressure levels and tight glycemic control have allowed improved survival of diabetic patients, the mortality excess remains unacceptably high in patients with diabetic nephropathy. New treatment strategies are under investigation, including inhibitors of AGE formation, protein kinase C inhibitors, antioxidants, glycosaminoglycans, PPAR-γ agonists and **COX-2 inhibitors**.

REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:246248 HCAPLUS
DOCUMENT NUMBER: 138:395253
TITLE: Advances in rheumatology: coxibs and beyond
AUTHOR(S): Kuritzky, Louis; Weaver, Arthur
CORPORATE SOURCE: Department of Community Health and Family Medicine, University of Florida, Gainesville, FL, USA
SOURCE: Journal of Pain and Symptom Management (2003), 25(2S), S6-S20
CODEN: JPSMEU; ISSN: 0885-3924
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Arthritis is a growing health concern in the US with approx. 70 million Americans currently affected. This figure will inevitably rise as the population ages. The pain and decreased mobility assocd. with arthritis have a significant impact on quality of life and because patients with arthritis are less active than the general population, they are at risk of addnl. conditions such as obesity, heart disease, **diabetes**, and hypertension. There are currently no disease modifying osteoarthritis (OA) drugs available; therefore anti-inflammatory, and/or analgesic medications such as acetaminophen and NSAIDs and simple analgesics form the mainstay of treatment. Coxibs may be preferred to traditional NSAIDs because of their improved gastrointestinal (GI) safety and tolerability profile. The use of topical agents may also be beneficial in some patients. In rheumatoid arthritis (RA) where disease modifying drugs (DMARDs) are available, anti-inflammatory agents such as NSAIDs and coxibs are used as adjuncts to disease modifying therapy. However, patients with RA are at increased risk of NSAID-related GI injury, particularly if they are also on corticosteroid medication.

Pharmacol. treatment of both RA and OA should be combined with appropriate nonpharmacol. modalities such as patient education, exercise programs, and joint motion and strengthening exercises. Such activities may delay joint degrdn. and help maintain phys. function.

REFERENCE COUNT: 74 THERE ARE 74 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L44 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:25471 HCAPLUS
DOCUMENT NUMBER: 136:240962
TITLE: Renal and cardiovascular effects of selective cyclooxygenase-2 inhibitors
AUTHOR(S): Komers, Radko; Anderson, Sharon; Epstein, Murray
CORPORATE SOURCE: Division of Nephrology, Hypertension, and Clinical Pharmacology, Oregon Health Sciences University, Portland, OR, USA
SOURCE: American Journal of Kidney Diseases (2001), 38(6), 1145-1157
CODEN: AJKDDP; ISSN: 0272-6386
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Selective inhibition of cyclooxygenase-2 (COX-2) was proposed as a novel anti-inflammatory and analgesic treatment with a reduced profile of gastrointestinal side effects compared with conventional nonsteroidal anti-inflammatory drugs (NSAIDs). Although perceived as an inducible enzyme by inflammatory and other stimuli, COX-2 is constitutively expressed in the kidney. In this review, we focus on renal and cardiovascular (CV) physiol. and pathophysiol. characteristics of COX-2 and renal and CV aspects of treatment with selective **COX-2 inhibitors**. Both clin. and exptl. studies have shown that renal and CV effects of **COX-2 inhibitors** are similar to those of NSAIDs. These effects include sodium, potassium, and water retention and decreases in renal function, as well as mild to modest increases in blood pressure (BP) and edema. These deleterious effects are amplified in patients with vol. and/or sodium depletion. The concomitant administration of **COX-2 inhibitors** may destabilize BP control in hypertensive patients treated with antihypertensive agents. In contrast to the normal kidney, which could constitute a target for adverse actions of **COX-2 inhibitors**, recent exptl. studies showed increased renal COX-2 expression in several models of renal injury, such as the remnant kidney, renovascular hypertension, and **diabetes**, and implicated COX-2 in the progression of renal failure. This suggests that **COX-2 inhibitors** may confer a renoprotective effect in diverse renal disorders. These intriguing formulations must be delineated further in appropriately designed prospective clin. trials.

REFERENCE COUNT: 74 THERE ARE 74 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

```
=> s l1 and myasthenia () gravis?
          3148 MYASTHENIA
             7 MYASTHENIAS
          3150 MYASTHENIA
                 (MYASTHENIA OR MYASTHENIAS)
          3410 GRAVIS?
          1618 GRS
          1618 GRS
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                (GRS)
          5028 GRAVIS?
                (GRAVIS? OR GRS)
          2980 MYASTHENIA (W) GRAVIS?
L45         23 L1 AND MYASTHENIA (W) GRAVIS?

=> s l45 and review/dt
       1734424 REVIEW/DT
L46          0 L45 AND REVIEW/DT

=> s l1 and multiple () sclerosis?
        325132 MULTIPLE
          3004 MULTIPLES
        327817 MULTIPLE
                (MULTIPLE OR MULTIPLES)
         18439 SCLEROSIS?
         10910 MULTIPLE (W) SCLEROSIS?
L47         39 L1 AND MULTIPLE (W) SCLEROSIS?

=> s l47 and review/dt
       1734424 REVIEW/DT
L48          0 L47 AND REVIEW/DT

=> s l1 and sorcoidosis?
             0 SORCOIDOSIS?
L49          0 L1 AND SORCOIDOSIS?

=> s l1 and nephrotic?
          3475 NEPHROTIC?
L50          4 L1 AND NEPHROTIC?

=> s l50 and review/dt
       1734424 REVIEW/DT
L51          2 L50 AND REVIEW/DT

=> d l51, ibib abs, 1-2

L51  ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2004 ACS on STN
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Full Text | Citing References

ACCESSION NUMBER: 2001:349750 HCAPLUS
DOCUMENT NUMBER: 135:220476
TITLE: Nonsteroidal anti-inflammatory drugs in systemic lupus erythematosus
AUTHOR(S): Ostensen, M.; Villiger, P. M.
CORPORATE SOURCE: Department of Rheumatology, Clinical Immunology and Allergy, University Hospital of Berne, Bern, Switz.
SOURCE: Lupus (2001), 10(3), 135-139
CODEN: LUPUES; ISSN: 0961-2033
PUBLISHER: Arnold, Hodder Headline
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 34 refs. Up to 80% of patients with systemic lupus erythematosus (SLE) are treated with nonsteroidal anti-inflammatory drugs (NSAID) for musculoskeletal symptoms, serositis and headache. This survey reviews the literature on non-selective and selective inhibitors of cyclooxygenases with an emphasis on the efficacy and safety profile reported in SLE patients. No lupus-specific data on gastro-intestinal side effects of NSAID exist. Both non-selective Cox-inhibitors and selective **Cox-2 inhibitors** induce renal side effects including

sodium retention and redn. of the glomerular filtration rate. Lupus nephritis is a risk factor for NSAID-induced acute renal failure, but not for rare idiosyncratic toxic renal reactions to NSAID. In refractory **nephrotic** syndrome, NSAID have been used successfully. Cutaneous and allergic reactions to NSAID are increased in SLE patients as well as hepatotoxic effects, particularly with high dose aspirin. Whereas a variety of central nervous system side effects of NSAID are probably no more common in SLE patients than in others, aseptic meningitis has been reported more frequently. Ovulation and pregnancy can be adversely affected by Cox-inhibitors. The antiplatelet effect of aspirin and non-selective Cox-inhibitors has a therapeutic potential in patients with the antiphospholipid syndrome (APS). In summary, treatment of SLE with NSAID requires awareness for the increased frequency of some side effects and close monitoring of toxicity.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L51 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2000:754174 HCAPLUS
DOCUMENT NUMBER: 134:320365
TITLE: Nonsteroidal anti-inflammatory drugs in systemic lupus erythematosus
AUTHOR(S): Ostensen, M.; Villiger, P. M.
CORPORATE SOURCE: Department of Rheumatology, Clinical Immunology and Allergy, University Hospital of Berne, Bern, CH-3010, Switz.
SOURCE: Lupus (2000), 9(8), 566-572
CODEN: LUPUES; ISSN: 0961-2033
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 60 refs. Up to 80% of patients with systemic lupus erythematosus (SLE) are treated with nonsteroidal antiinflammatory drugs (NSAID) for musculoskeletal symptoms, serositis and headache. This survey reviews the literature on non-selective and selective inhibitors of cyclooxygenases, with an emphasis on the efficacy and safety profile reported in SLE patients. No lupus-specific data on gastro-intestinal side effects of NSAID exist. Both non-selective Cox inhibitors and selective **Cox-2 inhibitors** induce renal side effects, including sodium retention and redn. of the glomerular filtration rate. Lupus nephritis is a risk factor for NSAID-induced acute renal failure, but not for rare idiosyncratic toxic renal reactions to NSAID. In refractory **nephrotic** syndrome, NSAID have been used successfully. Cutaneous and allergic reactions to NSAID are increased in SLE patients as well as hepatotoxic effects, particularly with high dose aspirin. Whereas a variety of central nervous system side effects of NSAID are probably no more common in SLE patients than others, aseptic meningitis has been reported more frequently. Ovulation and pregnancy can be adversely affected by Cox inhibitors. The antiplatelet effect of aspirin and non-selective Cox inhibitors has a therapeutic potential in patients with antiphospholipid syndrome (APS). In summary, treatment of SLE with NSAID requires awareness for the increased frequency of some side effects and close monitoring of toxicity.

REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s l1 and bechet?

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            45 BECHET?
L52          3 L1 AND BECHET?

=> s l52 and review/dt
       1734424 REVIEW/DT
L53          0 L52 AND REVIEW/DT

=> s l1 and polymyos?
           787 POLYMYOS?
L54         19 L1 AND POLYMYOS?

=> s l54 and review/dt
       1734424 REVIEW/DT
L55          0 L54 AND REVIEW/DT

=> s l1 and gingivitis?
          1708 GINGIVITIS?
L56         16 L1 AND GINGIVITIS?

=> s l56 and review/dt
       1734424 REVIEW/DT
L57          0 L56 AND REVIEW/DT

=> s l1 and conjunct?
         70848 CONJUNCT?
L58         34 L1 AND CONJUNCT?

=> s l58 and review/dt
       1734424 REVIEW/DT
L59          4 L58 AND REVIEW/DT

=> d l59, ibib abs, 1-4

L59  ANSWER 1 OF 4  HCAPLUS  COPYRIGHT 2004 ACS on STN
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Full Text | Citing References

ACCESSION NUMBER: 2003:988882 HCAPLUS
DOCUMENT NUMBER: 140:349806
TITLE: Paracetamol in the treatment of osteoarthritis pain
AUTHOR(S): Brandt, Kenneth
CORPORATE SOURCE: Departements de Rhumatologie et de Chirurgie Orthopedique, Faculte de Medecine, Universite d'Indiana et Centre pluridisciplinaire des maladies rhumatismales et osteoarticulaires de l'Universite d'Indiana, Etats-Unis, USA
SOURCE: Drugs (2003), 63(Spec. Issue), 23-41
CODEN: DRUGAY; ISSN: 0012-6667
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: French

AB A review. Osteoarthritis (OA) is the most common joint disease and OA of the knee, in particular, is the major cause of chronic disability among people >65 yr. Because nonsteroidal anti-inflammatory drugs (NSAIDs) improve symptoms in many patients with OA, it is widely considered that OA pain is due to synovial inflammation. However, OA pain may arise also from subchondral bone, the joint capsule, ligaments, tendons, entheses and periarticular muscle spasm. In many patients, the relief of OA pain and overall satisfaction with therapy may be as great with paracetamol (acetaminophen [APAP]) as with an NSAID. Cyclo-oxygenase (COX)-1-sparing NSAIDs (coxibs) are no more effective in the treatment of OA pain than

non-selective NSAIDs and, although they may significantly decrease the risk of serious adverse effects related to gastrointestinal ulcers (GI) and ulcer complications, their gastroprotective effect may be reduced by concomitant administration of low-dose aspirin. Also, they may increase the risk of myocardial infarction in predisposed individuals. Because coxibs do not inhibit platelet aggregation, if prophylaxis against thromboembolic disease is required in patients being treated with a selective **COX-2 inhibitor**, low-dose aspirin should be used in **conjunction** with the coxib. Furthermore, nonselective NSAIDs and coxibs may have adverse effects on the kidney, fracture healing and salt and water homeostasis. This paper discusses the relative positioning of APAP, NSAIDs and coxibs in the management of OA, on the basis of considerations of tolerability, efficacy and costs.

REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L59 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:856389 HCAPLUS
DOCUMENT NUMBER: 137:345467
TITLE: Selective cyclo-oxygenase-2 inhibitors and myocardial infarction: how strong is the link?
AUTHOR(S): Howes, Laurence G.; Krum, Henry
CORPORATE SOURCE: Department of Clinical Pharmacology, St. George Hospital, University of New South Wales, Kogarah, New South Wales, Australia
SOURCE: Drug Safety (2002), 25(12), 829-835
CODEN: DRSAEA; ISSN: 0114-5916
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. There are concerns that selective cyclo-oxygenase (**COX**)-**2 inhibitors** may be prothrombotic and increase the risk of myocardial infarction. This has largely arisen because of an unexpected finding of a higher rate of myocardial infarction in patients receiving rofecoxib compared with patients receiving naproxen in a study of gastrointestinal toxicity. The results of this study, a similar study of celecoxib vs. ibuprofen or diclofenac, and data obtained from a meta-anal. of aspirin (acetylsalicylic acid) primary prevention trials suggest that differences in the rates of myocardial infarction between rofecoxib and naproxen may have been due to an unexpectedly low rate of myocardial infarction in patients receiving naproxen. However, population surveillance data also suggest that rofecoxib may be assocd. with a greater risk of myocardial infarction than celecoxib and certain nonselective nonsteroidal anti-inflammatory drugs. The magnitude of this increase in risk, if real, is uncertain but it is likely to be relatively small in patients for whom cardiovascular prophylaxis with aspirin is not indicated. Patients who require nonsteroidal anti-inflammatory therapy for arthritis and who are at high risk of cardiovascular disease should receive aspirin, probably in **conjunction** with selective **COX-2 inhibitor** therapy, as the risk of gastrointestinal ulceration may be lower than for aspirin plus a nonselective nonsteroidal anti-inflammatory drug. In patients who do not require aspirin for the prevention of cardiovascular events, the lower risk of gastrointestinal ulceration assocd. with **COX-2 inhibitor** compared with non-selective nonsteroidal anti-inflammatory drugs would be expected to outweigh any increase in the risk of myocardial infarction, if one exists.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L59 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2000:257676 HCAPLUS
DOCUMENT NUMBER: 133:26379
TITLE: Less is more, regularly: metronomic dosing of cytotoxic drugs can target tumor angiogenesis in mice
AUTHOR(S): Hanahan, Douglas; Bergers, Gabriele; Bergsland, Emily
CORPORATE SOURCE: Department of Biochemistry and Biophysics, Hormone Research Institute, University of California San Francisco, San Francisco, CA, USA
SOURCE: Journal of Clinical Investigation (2000), 105(8), 1045-1047
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: American Society for Clinical Investigation
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 23 refs. Chemotherapeutic drugs, long the mainstay of cancer treatment, cause DNA damage and disrupt DNA replication in proliferating cells. Drug regimens have been designed to kill as many tumor cells as possible by treating with "max. tolerated doses" (MTD5) of these cytotoxic agents. Side effects such as neurotoxicity and damage to proliferating cells in healthy tissues pose serious constraints on the use of chemotherapy. The harsh side effects and the ultimate failures of most chemotherapies have fueled broad investigation of alternatives, including drugs that target not the transformed tumor cells themselves, but rather a genetically stable constituent cell type of tumors, the endothelial cells that form blood vessels. Angiogenesis, the process by which new blood vessels are formed, is a hallmark capability of cancer; a compelling body of evidence argues that tumor growth depends on the vasculature, and, in particular, on continuing angiogenesis. In particular, metronomic dosing with cytotoxic drugs, while demonstrably antiangiogenic, seem unlikely to prove efficacious in general as single agents. Nevertheless, we believe that metronomic delivery of lowered doses of cytotoxic drugs could be devised to minimize often devastating side effects of chemotherapy, while targeting endothelial and tumor cells. True efficacy may come only with combinatorial therapies, wherein novel cytotoxic dosing schedules are used in **conjunction** with other drugs or radiation. Possible combinations include other approved drugs, such as **cox-2 inhibitors**, thalidomide, or IFN-α/β, as well as exptl. drugs such as VEGF/ VEGF-receptor inhibitors, other angiogenesis inhibitors (e.g., TNP-470), proapoptotic drugs, or biotherapeutic agents such as oncolytic viruses. The possibilities raised by these studies are provocative and deserve further preclin. and clin. investigation.

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L59 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1999:669180 HCAPLUS
DOCUMENT NUMBER: 132:160652
TITLE: Celecoxib, a selective cyclooxygenase-2 inhibitor for the treatment of rheumatoid arthritis and osteoarthritis
AUTHOR(S): Goldenberg, Marvin M.
CORPORATE SOURCE: Mount Sinai NYU Health, New York, NY, USA
SOURCE: Clinical Therapeutics (1999), 21(9), 1497-1513
CODEN: CLTHDG; ISSN: 0149-2918

PUBLISHER: Excerpta Medica
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 56 refs. Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most frequently prescribed drugs, despite their well-established assocn. with gastroduodenal injury. Recent discovery of the cyclooxygenase (COX) isoenzymes COX-1 and COX-2 has improved our knowledge of the action of NSAIDs. COX-1 is continuously expressed in almost all tissues, where it converts arachidonate to the prostaglandins (PGs) important in homeostatic function; COX-2 is present in immune cells, blood vessel endothelial cells, and synovial fibroblasts. Classic NSAIDs inhibit both COX isoenzymes by occupying the cyclooxygenase-active site, preventing access by arachidonic acid. In theory, a drug such as celecoxib that selectively inhibited COX-2 might block inflammation, pain, and fever while reducing the side effects (gastric erosions and ulcers) assocd. with inhibition of COX-1. In animal models of inflammation and pain, celecoxib has shown marked suppression of PG prodn. and inflammation compared with indomethacin, the std. COX-1/**COX-2 inhibitor**. In clin. trials, celecoxib dosed at 100, 200, and 400 mg BID was found to significantly reduce the signs and symptoms of rheumatoid arthritis (RA) and osteoarthritis. In one RA study, celecoxib was found to be as clin. effective as diclofenac after 24 wk of treatment; at the end of the study, gastroduodenal ulcers occurred significantly more frequently in the diclofenac group (15%) than in the celecoxib group (4%). In a 1-wk endoscopy study comparing celecoxib with naproxen and placebo, the incidence of gastric erosions/ulcers was significantly greater in the naproxen group than in the celecoxib or placebo group. The most common adverse effects of celecoxib in clin. studies were headache, diarrhea, abdominal discomfort, and dizziness. Celecoxib has shown significant equiv. anti-inflammatory and analgesic efficacy and has produced less endoscopically apparent gastrointestinal (GI) ulceration or erosion than have 3 classic NSAIDs. Whether it will have long-term GI adverse effects or interact with other medications to cause serious adverse responses (eg, increased GI bleeding or rash in **conjunction** with other sulfonamide-like drugs) is unknown and remains to be established.
REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

```
=> s l1 and myocard? () ischemia?
         68813 MYOCARD?
         56950 ISCHEMIA?
          6978 MYOCARD? (W) ISCHEMIA?
L60          3 L1 AND MYOCARD? (W) ISCHEMIA?

=> s l60 and review/dt
       1734424 REVIEW/DT
L61          0 L60 AND REVIEW/DT

=> s l1 and conjunctiv?
          5863 CONJUNCTIV?
L62         10 L1 AND CONJUNCTIV?

=> s l62 and review/dt
       1734424 REVIEW/DT
L63          0 L62 AND REVIEW/DT

=> s l1 and cognitive () disorder?
         11978 COGNITIVE
        374069 DISORDER?
```

```
          500 COGNITIVE (W) DISORDER?
L64         1 L1 AND COGNITIVE (W) DISORDER?

=> d l64 and review/dt
'REVIEW' MUST END IN '/Q', '/A', '/L', '/S' OR '/B'
The saved name for a query (or structure or screen set) must end with
'/Q'.  The saved name for an answer set must end with '/A'.  The saved
name for an L# list must end with '/L'.  SDI request names must end
with '/S'.  To see a list of all saved query, answer set,, and L# list
names for this loginid, enter "DISPLAY SAVED" at an arrow
prompt (=>).  Enter "DISPLAY SAVED/S" to see a list of SDI request
names.  Enter "DISPLAY SAVED/B" to see a list of BATCH search
requests.

=> s l64 and review/dt
       1734424 REVIEW/DT
L65          0 L64 AND REVIEW/DT

=> s l1 and cognitive?
         12096 COGNITIVE?
L66         27 L1 AND COGNITIVE?

=> s l66 and review/dt
       1734424 REVIEW/DT
L67          6 L66 AND REVIEW/DT

=> d l167, ibib abs, 1-6
L167 NOT FOUND
The L-number entered has not been defined in this session, or it
has been deleted.  To see the L-numbers currently defined in this
session, enter DISPLAY HISTORY at an arrow prompt (=>).

=> d 167, ibib abs, 1-6

L67  ANSWER 1 OF 6  HCAPLUS  COPYRIGHT 2004 ACS on STN
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Full Text | Citing References

```
ACCESSION NUMBER:         2002:804187  HCAPLUS
DOCUMENT NUMBER:          138:202384
TITLE:                    Oxidative stress in brain aging Implications for
                          therapeutics of neurodegenerative diseases
AUTHOR(S):                Floyd, Robert A.; Hensley, Kenneth
CORPORATE SOURCE:         Free Radical Biology and Aging Research Program,
                          Oklahoma Medical Research Foundation, Oklahoma City,
                          OK, 73104, USA
SOURCE:                   Neurobiology of Aging (2002), 23(5), 795-807
                          CODEN: NEAGDO; ISSN: 0197-4580
PUBLISHER:                Elsevier Science Inc.
DOCUMENT TYPE:            Journal; General Review
LANGUAGE:                 English
AB   A review.  Age has a powerful effect on enhanced susceptibility to
     neurodegenerative diseases, including susceptibility to stroke and
     cognitive impairment (CI) even in optimally healthy individuals.  We
     critically evaluated the notion that oxidative stress increases in aging
     brain.  Rigorous studies show logarithmic age-dependent increases in
     oxidized proteins and oxidized DNA lesions.  Decreased activity of
     antioxidant protective enzymes does not account for the obsd. increases.
     The reactivity of the lipid oxidn. product 4-hydroxy-2-nonenal (HNE) with
     key mitochondria enzymes may be important in the age-dependent loss in
     energy generation and enhanced susceptibility of neurons to apoptosis.
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Age-dependent enhanced neuroinflammatory processes may play an important role in toxin generation that causes death or dysfunction of neurons in neurodegenerative diseases. Non-steroidal anti-inflammatory drugs (NSAIDs) show significant promise. Vitamin E supplementation did not show major beneficial effect on **cognitive** functions. Major clin. trials for Alzheimer's disease (AD) involving cycloxygenase-II (COX II) inhibitors and amyloid-beta vaccination have been discontinued. Novel therapeutics based on blocking neuron damaging neuroinflammatory processes show great promise for abating dementia progression although they have yet to make it to clin. practice.

REFERENCE COUNT: 121 THERE ARE 121 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L67 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:795379 HCAPLUS
DOCUMENT NUMBER: 138:313675
TITLE: From cyclooxygenase activities to Alzheimer's disease neuropathology: experimental approaches and therapeutic interventions
AUTHOR(S): Pasinetti, Giulio Maria
CORPORATE SOURCE: Neuroinflammation Research Laboratories, Department of Psychiatry, Mount Sinai School of Medicine, New York, NY, 10029, USA
SOURCE: Drug Development Research (2002), 56(3), 438-445
CODEN: DDREDK; ISSN: 0272-4391
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Several prospective and retrospective epidemiol. studies have demonstrated a protective effect for antiinflammatory drugs in Alzheimer's disease (AD). However, despite this evidence therapeutic studies investigating nonsteroidal antiinflammatory drugs (NSAIDs), including cyclooxygenase (COX)-1 and **COX-2 inhibitors** and steroids, do not support this hypothesis. This discrepancy may be due to the fact that the bulk of epidemiol. evidence has examd. the likely incidence of AD prior to the onset of clin. symptoms of disease. In contrast, in therapeutic studies NSAIDs are administered to patients with illnesses severe enough to exceed the clin. detection threshold, suggesting that NSAID therapy administered following the onset of AD may not be optimally effective. Thus, patients at high risk for AD, e.g., those with mild **cognitive** impairment (MCI), may be more suitable for study in clin. trials of NSAIDs. Indeed, recent evidence suggests that different indexes of classical inflammatory cascades have distinct assocns. with different phases of the clin. progression of AD. In this review, I discuss the potential role of inflammation in the clin. progression of AD and how this evidence relates to preventive use of antiinflammatory drugs for AD treatment. I then examine the importance of evidence for the potential role of inflammation in amyloidosis in the AD brain and exptl. models. I consider the implications of inflammation in AD and recent evidence potentially supporting a neg. role of inflammation in vaccination therapy trials. In conclusion, I examine cutting-edge clin. studies investigating NSAID therapy for AD.

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L67 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:411415 HCAPLUS
DOCUMENT NUMBER: 137:179252
TITLE: Evaluation of selective **COX-2 inhibitors** for the treatment of Alzheimer's disease
AUTHOR(S): Aisen, Paul S.
CORPORATE SOURCE: Departments of Neurology and Medicine, Georgetown University Medical Center, Washington, DC, 20007, USA
SOURCE: Journal of Pain and Symptom Management (2002), 23(4S), S35-S40
CODEN: JPSMEU; ISSN: 0885-3924
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Alzheimer's disease (AD) is a worldwide problem that affects 5 million people in the United States alone. Until the approval of tacrine in the mid-1990s, there was no effective therapy for the **cognitive** symptoms of AD. Although cholinergic therapy provides modest but significant symptomatic relief, the development of effective disease-modifying therapy is essential. It has been demonstrated that a no. of inflammatory processes are active in the brain of patients with AD, and therefore it is believed that an anti-inflammatory regimen may offer some degree of neuroprotection. Several studies have indicated that use of nonsteroidal anti-inflammatory drugs (NSAIDs) is assocd. with delayed onset and/or slowed **cognitive** decline in AD. Although not currently approved for this condition, recent findings have demonstrated that cyclooxygenase (COX)-2 is of primary importance in the inflammatory response and may have a role in neurodegeneration. Therefore, selective **COX-2 inhibitors** (coxibs) may have an advantage over traditional NSAIDs as potential therapeutic agents in AD. The Alzheimer's Disease Cooperative Study (ADCS) is conducting an ongoing multicenter, double-blind, placebo-controlled trial to det. whether rofecoxib, a coxib, or naproxen, a nonselective NSAID, will slow the rate of **cognitive** and clin. decline in AD. This study, along with other clin. studies currently under way, will det. the utility of selective and nonselective COX inhibitors for the prevention and treatment of AD.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L67 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:266015 HCAPLUS
DOCUMENT NUMBER: 135:40287
TITLE: The status of ongoing trials for mild **cognitive** impairment
AUTHOR(S): Sramek, John J.; Veroff, Amy E.; Cutler, Neal R.
CORPORATE SOURCE: California Clinical Trials, Beverly Hills, CA, USA
SOURCE: Expert Opinion on Investigational Drugs (2001), 10(4), 741-752
CODEN: EOIDER; ISSN: 1354-3784
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 82 refs. Mild **cognitive** impairment (MCI) is a term used to describe memory decline or other specific **cognitive** impairment in individuals who do not have dementia or significant impairment of other **cognitive** functions beyond that expected for their age or education. It has been suggested that as much as 38% of the elderly population would

meet criteria for MCI and although the assocd. memory deficits are mild, the fact that up to 15% of MCI patients, particularly those with a particular type of memory impairment, convert to Alzheimer's disease (AD) annually has prompted serious attention. Despite the high conversion rate, MCI cannot be used synonymously with early or mild AD, as patients with AD are impaired not only in memory performance but in other **cognitive** domains as well; they meet diagnostic criteria for dementia. However, since there is a high conversion rate from MCI to AD, it is likely many with MCI have the underlying neuropathol. of AD, though they do not yet meet clin. diagnostic criteria. Therefore, treatment strategies developed for AD, specifically acetylcholinesterase inhibitors and **Cox-2 inhibitors**, have been among the first employed to treat MCI. It is hoped that by impeding the progression of MCI in this manner, fewer patients will convert to AD. This article will give a brief overview of the condition of mild **cognitive** impairment and an account of trial methodol. and current treatment strategies being employed for MCI.

REFERENCE COUNT: 82 THERE ARE 82 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L67 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2000:251152 HCAPLUS
DOCUMENT NUMBER: 133:12237
TITLE: Anti-inflammatory drugs: a hope for Alzheimer's disease?
AUTHOR(S): Hull, Michael; Lieb, Klaus; Fiebich, Bernd L.
CORPORATE SOURCE: Department of Psychiatry and Psychotherapy, University of Freiburg Medical School, Freiburg, D-79104, Germany
SOURCE: Expert Opinion on Investigational Drugs (2000), 9(4), 671-683
CODEN: EOIDER; ISSN: 1354-3784
PUBLISHER: Ashley Publications
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 123 refs. Human brain cells are capable of initiating and amplifying a brain specific inflammatory response involving the synthesis of cytokines, acute-phase proteins, complement proteins, prostaglandins and oxygen radicals. In Alzheimer's disease (AD), all signs of an inflammatory microglial and astroglial activation are present inside and outside amyloid depositions and along axons of neurons with neurofibrillary tangles. Cell culture and animal models suggest a bidirectional relationship between inflammatory activation of glial cells and the deposition of amyloid. Although it remains unclear which of the different pathophysiol. processes in AD may be the driving force in an individual case, the inflammatory activation may increase the speed of **cognitive** decline. Epidemiol. studies point to a reduced risk of AD among users of anti-inflammatory drugs. Therefore, anti-inflammatory drugs have become the focus of several new treatment strategies. A clin. trial with the non-steroidal anti-inflammatory drug (NSAID) indomethacin showed promising results, while a clin. trial with steroids did not show a beneficial effect. Further trials with NSAIDs such as unselective cyclooxygenase (COX) and selective cyclooxygenase-2 (**COX-2**) **inhibitors** are on their way. COX inhibitors may not only act on microglial and astroglial cells but also reduce neuronal prostaglandin prodn. New data suggest that prostaglandins enhance neurotoxicity or induce pro-inflammatory cytokine synthesis in astroglial cells. Amongst these promising new strategies to reduce microglial or monocyte activation, interfering with intracellular pathways has been shown to be effective in various cell culture and animal models but clin. studies have

not yet been performed.
REFERENCE COUNT: 123 THERE ARE 123 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L67 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1999:397414 HCAPLUS
DOCUMENT NUMBER: 131:67542
TITLE: The clinical potential of cyclooxygenase-2-specific inhibitors
AUTHOR(S): Lipsky, Peter E.
CORPORATE SOURCE: Rheumatic Diseases Division, Harold C. Simmons Arthritis Research Center, The University of Texas Southwestern Medical Center at Dallas, Dallas, TX, 75235, USA
SOURCE: American Journal of Medicine (1999), 106(5B), 51S-57S
CODEN: AJMEAZ; ISSN: 0002-9343
PUBLISHER: Excerpta Medica, Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 51 refs. Emerging evidence suggests that cyclooxygenase-2 (COX-2) has diverse physiol. and pathophysiol. functions. It is expressed constitutively in the developing kidney and brain, playing a role in their proper maturation and function. Further, COX-2 expression may be up-regulated at certain sites: in the kidney during sodium restriction; in the microglia of **cognitive** centers within the hippocampus and cortex in Alzheimer's disease; and in intestinal adenomas and colon tumors. On the basis of COX-2 expression in Alzheimer's disease and colon cancer, COX-2-specific inhibitors may find clin. utility in the prevention or treatment of these conditions. Despite this apparently optimistic outlook for future uses of **COX-2 inhibitors**, most of the findings supporting this perspective are based on in vitro and in vivo models and must be rigorously corroborated in human studies, some of which are already planned.
REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> s l1 and senile () dement?
          6071 SENILE
            10 SENILES
          6076 SENILE
                 (SENILE OR SENILES)
          9873 DEMENT?
          1185 SENILE (W) DEMENT?
L68          0 L1 AND SENILE (W) DEMENT?

=> s l1 and senil? () dement?
         21302 SENIL?
          9873 DEMENT?
          1189 SENIL? (W) DEMENT?
L69          0 L1 AND SENIL? (W) DEMENT?

=> s l1 and senile
          6071 SENILE
            10 SENILES
          6076 SENILE
                 (SENILE OR SENILES)
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L70         16 L1 AND SENILE

=> s l70 and review/dt
       1734424 REVIEW/DT
L71           0 L70 AND REVIEW/DT

=> s l1 and dementia?
          9442 DEMENTIA?
L72          21 L1 AND DEMENTIA?

=> s l72 and review/dt
       1734424 REVIEW/DT
L73           5 L72 AND REVIEW/DT

=> d l73, ibib abs, 1-5

L73  ANSWER 1 OF 5  HCAPLUS  COPYRIGHT 2004 ACS on STN
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Full Text | Citing References

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ACCESSION NUMBER:         2003:33554  HCAPLUS
DOCUMENT NUMBER:          139:46145
TITLE:                    Cyclooxygenase as a Target for the Antiamyloidogenic
                          Activities of Nonsteroidal Anti-Inflammatory Drugs in
                          Alzheimer's Disease
AUTHOR(S):                Pasinetti, Giulio Maria
CORPORATE SOURCE:         Department of Psychiatry, Neuroinflammation Research
                          Laboratories, Mount Sinai Medical Center, New York,
                          NY, USA
SOURCE:                   Neurosignals (2002), 11(5), 293-297
                          CODEN: NEURIQ; ISSN: 1424-862X
PUBLISHER:                S. Karger AG
DOCUMENT TYPE:            Journal; General Review
LANGUAGE:                 English
AB    A review.  A large no. of epidemiol. studies have addressed the possible
      protective effect of anti-inflammatory drug use with regard to Alzheimer's
      disease (AD).  The most convincing of these studies - the Baltimore
      Longitudinal Study of Aging - utilized data collected prospectively,
      thereby minimizing recall bias issues.  However, despite this evidence,
      therapeutic studies investigating nonsteroidal anti-inflammatory drugs
      (NSAIDs), including cyclooxygenase-1 (COX-1) and COX-2 inhibitors
      and steroids, do not support this hypothesis.  This discrepancy may be due
      to the fact that the bulk of epidemiol. evidence has examd. the likely
      incidence of AD prior to the onset of clin. symptoms of disease.  On the
      basis of this information, the article will attempt to formulate a
      possible scenario, in which optimal NSAIDs might be tested in the most
      favorable clin. therapeutic conditions in order to det. whether NSAIDs can
      provide beneficial treatment for the clin. progression of AD dementia.
REFERENCE COUNT:          43    THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L73  ANSWER 2 OF 5  HCAPLUS  COPYRIGHT 2004 ACS on STN
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Full Text | Citing References

```
ACCESSION NUMBER:         2002:804187  HCAPLUS
DOCUMENT NUMBER:          138:202384
TITLE:                    Oxidative stress in brain aging Implications for
                          therapeutics of neurodegenerative diseases
AUTHOR(S):                Floyd, Robert A.; Hensley, Kenneth
CORPORATE SOURCE:         Free Radical Biology and Aging Research Program,
                          Oklahoma Medical Research Foundation, Oklahoma City,
```

OK, 73104, USA
SOURCE: Neurobiology of Aging (2002), 23(5), 795-807
CODEN: NEAGDO; ISSN: 0197-4580
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. Age has a powerful effect on enhanced susceptibility to neurodegenerative diseases, including susceptibility to stroke and cognitive impairment (CI) even in optimally healthy individuals. We critically evaluated the notion that oxidative stress increases in aging brain. Rigorous studies show logarithmic age-dependent increases in oxidized proteins and oxidized DNA lesions. Decreased activity of antioxidant protective enzymes does not account for the obsd. increases. The reactivity of the lipid oxidn. product 4-hydroxy-2-nonenal (HNE) with key mitochondria enzymes may be important in the age-dependent loss in energy generation and enhanced susceptibility of neurons to apoptosis. Age-dependent enhanced neuroinflammatory processes may play an important role in toxin generation that causes death or dysfunction of neurons in neurodegenerative diseases. Non-steroidal anti-inflammatory drugs (NSAIDs) show significant promise. Vitamin E supplementation did not show major beneficial effect on cognitive functions. Major clin. trials for Alzheimer's disease (AD) involving cycloxygenase-II (COX II) inhibitors and amyloid-beta vaccination have been discontinued. Novel therapeutics based on blocking neuron damaging neuroinflammatory processes show great promise for abating **dementia** progression although they have yet to make it to clin. practice.
REFERENCE COUNT: 121 THERE ARE 121 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L73 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN
Full Text | Citing References
ACCESSION NUMBER: 2001:554480 HCAPLUS
DOCUMENT NUMBER: 135:326832
TITLE: The clinical developments and future of the **COX-2 inhibitor** drugs
AUTHOR(S): Goldstein, Jerome
CORPORATE SOURCE: San Francisco Clinical Research Center, San Francisco, CA, 94109, USA
SOURCE: Inflammopharmacology (2001), 9(1-2), 91-99
CODEN: IAOAES; ISSN: 0925-4692
PUBLISHER: VSP BV
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review, with refs. A new era of analgesia began with the discovery of aspirin in 1899. Since that time, many newer NSAIDs (non-steroid anti-inflammatory drugs) have been discovered and utilized in clin. practice. The mechanism of anti-inflammatory action of NSAIDs is believed to result from inhibition of the enzyme cyclooxygenase (COX), discovered in the 1970s. This enzyme represents the key rate-limiting step in the prodn. of prostaglandins (PGs) from arachidonic acid. Since PGs are essential for normal gastrointestinal, renal, and platelet function, as well as mediating the inflammatory process, inhibition of cyclooxygenase has both beneficial and deleterious effects. The beneficial effect, obviously, is inhibition of the inflammatory process, while the harmful effects comprise an increased incidence of upper gastrointestinal toxicity (ulceration, perforation, and bleeding) as well as possible renal and platelet dysfunction. In the late 1980s, it was discovered that two isoforms of cyclooxygenase existed (COX-1 and COX-2). COX-1 represents a

constitutive form that is expressed in most tissues. In contrast, COX-2 is induced at sites of inflammation and also occurs under normal circumstances in the brain and renal tissues. Since COX-2 levels increase dramatically during acute and chronic inflammation, it was hypothesized that the **COX-2 inhibitors** might offer significant anti-inflammatory qualities with reduced toxicity and may have utility in central nervous system mediated conditions other than peripheral pain, including **dementias** such as Alzheimer's disease and headache, specifically, migraine headache.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L73 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:266015 HCAPLUS
DOCUMENT NUMBER: 135:40287
TITLE: The status of ongoing trials for mild cognitive impairment
AUTHOR(S): Sramek, John J.; Veroff, Amy E.; Cutler, Neal R.
CORPORATE SOURCE: California Clinical Trials, Beverly Hills, CA, USA
SOURCE: Expert Opinion on Investigational Drugs (2001), 10(4), 741-752
CODEN: EOIDER; ISSN: 1354-3784
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 82 refs. Mild cognitive impairment (MCI) is a term used to describe memory decline or other specific cognitive impairment in individuals who do not have **dementia** or significant impairment of other cognitive functions beyond that expected for their age or education. It has been suggested that as much as 38% of the elderly population would meet criteria for MCI and although the assocd. memory deficits are mild, the fact that up to 15% of MCI patients, particularly those with a particular type of memory impairment, convert to Alzheimer's disease (AD) annually has prompted serious attention. Despite the high conversion rate, MCI cannot be used synonymously with early or mild AD, as patients with AD are impaired not only in memory performance but in other cognitive domains as well; they meet diagnostic criteria for **dementia**. However, since there is a high conversion rate from MCI to AD, it is likely many with MCI have the underlying neuropathol. of AD, though they do not yet meet clin. diagnostic criteria. Therefore, treatment strategies developed for AD, specifically acetylcholinesterase inhibitors and **Cox-2 inhibitors**, have been among the first employed to treat MCI. It is hoped that by impeding the progression of MCI in this manner, fewer patients will convert to AD. This article will give a brief overview of the condition of mild cognitive impairment and an account of trial methodol. and current treatment strategies being employed for MCI.

REFERENCE COUNT: 82 THERE ARE 82 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L73 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2000:147372 HCAPLUS
DOCUMENT NUMBER: 132:273659
TITLE: New anti-inflammatory treatment strategy in Alzheimer's disease
AUTHOR(S): Sugaya, Kiminobu; Uz, Tolga; Kumar, Vinod; Manev, Hari
CORPORATE SOURCE: The Psychiatric Institute, West Side VA Medical

Center, Department of Psychiatry, University of Illinois at Chicago, Chicago, IL, 60612, USA
SOURCE: Japanese Journal of Pharmacology (2000), 82(2), 85-94
CODEN: JJPAAZ; ISSN: 0021-5198
PUBLISHER: Japanese Pharmacological Society
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 111 refs. Numerous reports have indicated that patients suffering from inflammatory diseases (e.g., arthritis) who take anti-inflammatory medication have a reduced risk of developing Alzheimer's disease (AD). Thus, the first generation of anti-inflammatory cyclooxygenase (COX) inhibitors, such as aspirin and indomethacin, have been tested as potential therapeutics in AD. Because the inhibition of COX-1 is also known to cause tissue damage in the gastrointestinal system from the resultant reduced cytoprotection, selective **COX-2 inhibitors** are being investigated and tested clin. as potentially better therapeutics for AD patients. However, such drugs may also trigger unwanted effects; for example, the **COX-2 inhibitors**, which reduce the prodn. of one type of eicosanoids, the prostaglandins, may increase the prodn. of other eicosanoids; i.e., the leukotriene B4 (LTB4), which is one of the most potent endogenous chemotactic/inflammatory factors. LTB4 prodn. is initiated by the enzyme 5-lipoxygenase (5-LOX). The expression of the 5-LOX gene is upregulated during neurodegeneration and with aging. In spite of the fact that 5-LOX and leukotrienes are major players in the inflammation cascade, their role in AD pathobiol./therapy has not been extensively investigated. We propose that the 5-LOX inflammatory cascade may take part in the process of aging-assocd. neurodegenerative diseases, and we point to the role of 5-LOX in neurodegeneration and discuss its relevance for anti-inflammatory therapy of AD.
REFERENCE COUNT: 111 THERE ARE 111 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> s l1 and pick? () disease
         59143 PICK?
        686545 DISEASE
        191032 DISEASES
        776485 DISEASE
                  (DISEASE OR DISEASES)
           799 PICK? (W) DISEASE
L74          0 L1 AND PICK? (W) DISEASE

=> s l1 and pick's?
MISMATCHED QUOTE 'PICK'S?'
Quotation marks (or apostrophes) must be used in pairs,
one before and one after the expression you are setting
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=> s l1 and pick?
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L75          2 L1 AND PICK?

=> s l75 and review/dt
       1734424 REVIEW/DT
L76          0 L75 AND REVIEW/DT

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          4973 HUNTINGTON?
          4023 CHOREA?
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           255 HUNTINGTON? (W) CHOREA?
L77          0 L1 AND HUNTINGTON? (W) CHOREA?

=> s l1 and huntington?
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L78         13 L1 AND HUNTINGTON?

=> s l78 and review/dt
       1734424 REVIEW/DT
L79          0 L78 AND REVIEW/DT

=> s l1 and parkinson?
         18292 PARKINSON?
L80         22 L1 AND PARKINSON?

=> s l80 and review/dt
       1734424 REVIEW/DT
L81          0 L80 AND REVIEW/DT

=> s l1 and creutzfelt?
             1 CREUTZFELT?
L82          0 L1 AND CREUTZFELT?

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          1323 CREUTZFEL?
L83          0 L1 AND CREUTZFEL?

=> s l1 and trauma?
         17261 TRAUMA?
L84         36 L1 AND TRAUMA?

=> s l84 and review/dt
       1734424 REVIEW/DT
L85          3 L84 AND REVIEW/DT

=> d l85, ibib abs, `-3
'`-3' IS NOT A VALID FORMAT FOR FILE 'HCAPLUS'

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ABS --------- GI and AB
ALL --------- BIB, AB, IND, RE
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BIB --------- AN, plus Bibliographic Data and PI table (default)
CAN --------- List of CA abstract numbers without answer numbers
CBIB -------- AN, plus Compressed Bibliographic Data
DALL -------- ALL, delimited (end of each field identified)
DMAX -------- MAX, delimited for post-processing
FAM --------- AN, PI and PRAI in table, plus Patent Family data
FBIB -------- AN, BIB, plus Patent FAM
IND --------- Indexing data
IPC --------- International Patent Classifications
MAX --------- ALL, plus Patent FAM, RE
PATS -------- PI, SO
SAM --------- CC, SX, TI, ST, IT
SCAN -------- CC, SX, TI, ST, IT (random display, no answer numbers;
              SCAN must be entered on the same line as the DISPLAY,
              e.g., D SCAN or DISPLAY SCAN)
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IABS -------- ABS, indented with text labels
IALL -------- ALL, indented with text labels
IBIB -------- BIB, indented with text labels
IMAX -------- MAX, indented with text labels
ISTD -------- STD, indented with text labels

OBIB -------- AN, plus Bibliographic Data (original)
OIBIB ------- OBIB, indented with text labels

SBIB -------- BIB, no citations
SIBIB ------- IBIB, no citations

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HITIND ------ IC, ICA, ICI, NCL, CC and index field (ST and IT)
              containing hit terms
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HITSTR ------ HIT RN, its text modification, its CA index name, and
              its structure diagram
HITSEQ ------ HIT RN, its text modification, its CA index name, its
              structure diagram, plus NTE and SEQ fields
FHITSTR ----- First HIT RN, its text modification, its CA index name, and
              its structure diagram
FHITSEQ ----- First HIT RN, its text modification, its CA index name, its
              structure diagram, plus NTE and SEQ fields
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OCC --------- Number of occurrence of hit term and field in which it occurs

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     (FILE 'HOME' ENTERED AT 10:48:57 ON 15 JUN 2004)

     FILE 'REGISTRY' ENTERED AT 10:49:17 ON 15 JUN 2004

     FILE 'HCAPLUS' ENTERED AT 10:49:39 ON 15 JUN 2004
L1          2615 S COX-2 () INHIBIT?
L2          1536 S L1 AND INFLAMMAT?
L3           434 S L2 AND REVIEW/DT
L4            22 S L1 AND INFLAMMAT? () DISORDER?
L5             6 S L4 AND REVIEW/DT
L6            41 S L1 AND ULCERAT? () COLIT?
L7             1 S L6 AND REVIEW/DT
L8            72 S L1 AND ASTHMA?
L9            12 S L8 AND REVIEW/DT
L10           56 S L1 AND CROHN?
L11            1 S L10 AND REVIEW/DT
L12           33 S L1 AND GASTRIT?
L13            5 S L12 AND REVIEW/DT
L14            0 S L1 AND VASCUL () DISEASE
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L15          9 S L1 AND VASCUL? () DISEASE?
L16          3 S L15 AND REVIEW/DT
L17         15 S L1 AND ALLERGIC () RHINIT?
L18          0 S L17 AND REVIEW/DT
L19         71 S L1 AND ALLER?
L20          4 S L19 AND REVIEW/DT
L21          9 S L1 AND IRRIT? () BOWEL? () SYNDROME?
L22          0 S L21 AND REVIEW/DT
L23          9 S L1 AND IRRIT? () BOWEL?
L24         31 S L1 AND MIGRAINE
L25          2 S L24 AND REVIEW/DT
L26          0 S L1 AND PERIARTERITS? () NODOS?
L27         14 S L1 AND PERIART?
L28          2 S L27 AND REVIEW/DT
L29          0 S L1 AND THYROIDITS?
L30         27 S L1 AND THYROID?
L31          0 S L30 AND REVIEW/DT
L32          0 S L1 AND APLASTIC? () ANEMIA?
L33          1 S L1 AND APLAST?
L34          0 S L33 AND REVIEW/DT
L35          0 S L1 AND HODGIN? () DISEASE?
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L37          6 S L1 AND HODGKIN?
L38          0 S L37 AND REVIEW/DT
L39          0 S L37 AND SLERODOM?
L40          0 S L1 AND SCLERODOM?
L41         59 S L1 AND SCLERO?
L42          1 S L41 AND REVIEW/DT
L43         59 S L1 AND DIABETE?
L44          4 S L43 AND REVIEW/DT
L45         23 S L1 AND MYASTHENIA () GRAVIS?
L46          0 S L45 AND REVIEW/DT
L47         39 S L1 AND MULTIPLE () SCLEROSIS?
L48          0 S L47 AND REVIEW/DT
L49          0 S L1 AND SORCOIDOSIS?
L50          4 S L1 AND NEPHROTIC?
L51          2 S L50 AND REVIEW/DT
L52          3 S L1 AND BECHET?
L53          0 S L52 AND REVIEW/DT
L54         19 S L1 AND POLYMYOS?
L55          0 S L54 AND REVIEW/DT
L56         16 S L1 AND GINGIVITIS?
L57          0 S L56 AND REVIEW/DT
L58         34 S L1 AND CONJUNCT?
L59          4 S L58 AND REVIEW/DT
L60          3 S L1 AND MYOCARD? () ISCHEMIA?
L61          0 S L60 AND REVIEW/DT
L62         10 S L1 AND CONJUNCTIV?
L63          0 S L62 AND REVIEW/DT
L64          1 S L1 AND COGNITIVE () DISORDER?
L65          0 S L64 AND REVIEW/DT
L66         27 S L1 AND COGNITIVE?
L67          6 S L66 AND REVIEW/DT
L68          0 S L1 AND SENILE () DEMENT?
L69          0 S L1 AND SENIL? () DEMENT?
L70         16 S L1 AND SENILE
L71          0 S L70 AND REVIEW/DT
L72         21 S L1 AND DEMENTIA?
L73          5 S L72 AND REVIEW/DT
L74          0 S L1 AND PICK? () DISEASE
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L75           2 S L1 AND PICK?
L76           0 S L75 AND REVIEW/DT
L77           0 S L1 AND HUNTINGTON? () CHOREA?
L78          13 S L1 AND HUNTINGTON?
L79           0 S L78 AND REVIEW/DT
L80          22 S L1 AND PARKINSON?
L81           0 S L80 AND REVIEW/DT
L82           0 S L1 AND CREUTZFELT?
L83           0 S L1 AND CREUTZFEL?
L84          36 S L1 AND TRAUMA?
L85           3 S L84 AND REVIEW/DT

=> d l85, ibib abs, 1-3

L85  ANSWER 1 OF 3  HCAPLUS  COPYRIGHT 2004 ACS on STN
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Full Text | Citing References

ACCESSION NUMBER: 2001:714219 HCAPLUS
DOCUMENT NUMBER: 136:747
TITLE: Identification of a novel P2 receptor associated with cyclooxygenase-2 upregulation and reactive astrogliosis
AUTHOR(S): Brambilla, Roberta; Schiller, Paul; D'Ippolito, Gianluca; Neary, Joseph T.; Burnstock, Geoffrey; Cattabeni, Flaminio; Abbracchio, Maria P.
CORPORATE SOURCE: Institute of Pharmacological Sciences, University of Milan, Milan, 20133, Italy
SOURCE: Drug Development Research (2001), 53(2/3), 148-157
CODEN: DDREDK; ISSN: 0272-4391
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review, with refs. Astrocytes respond to **trauma** and ischemia with reactive astrogliosis. Although beneficial under certain conditions, excessive gliosis may be detrimental and contribute to neuronal death in neurodegenerative diseases. To evaluate the hypothesis that ATP may act as a trigger of reactive gliosis, we tested α,βmethylene-ATP (α,βmeATP) in an in vitro exptl. model (rat brain astrocytic cultures), where astrogliosis can be quantified as elongation of astrocytic processes, an event that reproduces one of the main hallmarks of in vivo gliosis. The α,βmeATP induced a concn.-dependent elongation of astrocytic processes, an effect which was counteracted by the P2 receptor antagonists suramin and pyridoxal phosphate-6-azophenyl-2',4'-disulfonic acid (PPADS). Signaling studies revealed that α,βmeATP-induced gliosis is mediated by a G-protein-coupled receptor (a P2Y receptor) characterized by an "atypical" pharmacol. profile and coupled to an early release of arachidonic acid. In an earlier study we showed that challenge of cells with α,βmeATP also resulted in upregulation of inducible cyclooxygenase-2 (COX-2), whose activity has been reported to be pathol. elevated in neurodegenerative diseases characterized by inflammation and astrocytic activation. Upregulation of COX-2 by α,βmeATP was causally related to reactive astrogliosis in vitro, since the selective **COX-2 inhibitor** NS-398 prevented both purine-induced elongation of astrocytic processes and the assocd. increase in COX-2 protein levels. Preliminary data on the putative receptor-to-nucleus pathways responsible for purine-induced gliosis suggest that upregulation of COX-2 may occur through the protein kinase C / mitogen-activated protein kinase system and may involve the formation of AP-1 transcription complexes. We speculate that antagonists

selective for this novel P2Y receptor subtype may represent a new class of neuroprotective agents able to reduce neurodegeneration by counteracting the inflammatory events contributing to neuronal cell death.

REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L85 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:427626 HCAPLUS
DOCUMENT NUMBER: 135:251307
TITLE: Pharmacology of **COX-2 inhibition** in man: Antinflammatory and analgesic effects of nimesulide
AUTHOR(S): Fitzgerald, D.; McCrory, C.
CORPORATE SOURCE: Department of Clinical Pharmacology, Royal College of Surgeons in Ireland, Dublin, Ire.
SOURCE: Drugs of Today (2001), 37(Suppl. B, Nimesulide), 15-20
CODEN: MDACAP; ISSN: 0025-7656
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 35 refs. The clin. effects of cyclooxygenase 2 (**COX-2**) **inhibitors** in arthritis are being studied, particularly their potential for reducing risk from conventional nonsteroidal antiinflammatory drugs (NSAIDs). COX-2 is expressed in the hypertrophied synovial tissue of patients with rheumatoid arthritis and studies show that it is responsible for prostaglandin generation in the joint following surgical **trauma**. Further data suggest that prostaglandins play a role in pain perception by regulating opioid receptors and that removal of prostaglandins enhances opioid receptor signaling. Nimesulide has been found to exhibit a high degree of selectivity for COX-2 in vitro and in vivo. In patients undergoing thoracotomy, nimesulide provided better pain relief than opiates alone and reduced the need for opiates. Since nimesulide has no effect on platelet or gastric prostaglandin formation and induces less gastric and small bowel injury than conventional NSAIDs, it would have an advantage over NSAIDs in postoperative patients. While there are still a no. of outstanding questions on the safety of COX-2 selective inhibitors, they are proving to be as effective as NSAIDs in a variety of clin. conditions and have been helpful in understanding the role of COX-2 in clin. disease.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L85 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1997:645432 HCAPLUS
DOCUMENT NUMBER: 127:305962
TITLE: Brain COX-2 in experimental models of epilepsy and stroke: signalling pathways leading to enhanced expression
AUTHOR(S): Bazan, N. G.; Marcheselli, V. M.; Allan, G.; Van Meter, K.; Moises, J. P.
CORPORATE SOURCE: LSU Neuroscience Center, School of Medicine, Louisiana State University Medical Center, New Orleans, LA, 70112, USA
SOURCE: New Targets in Inflammation: Inhibitors of COX-2 or Adhesion Molecules, Proceedings of a Conference, New Orleans, Apr. 15-16, 1996 (1996), 47-53. Editor(s): Bazan, Nicolas G.; Botting, Jack H.; Vane, John R.

Kluwer: Dordrecht, Neth.
CODEN: 65DFA5
DOCUMENT TYPE: Conference; **General Review**
LANGUAGE: English
AB A review, with 32 refs. Topics discussed include: inducible prostaglandin synthase in the brain, induction of COX-2 in neurotrauma in relation to platelet-activating factor (PAF), a PAF-responsive element in the COX-2 promoter, PAF receptors and signal transduction, and **COX-2 inhibition** as a new strategy for neuroprotection.

=> **s l1 and infection?**
237333 INFECTION?
L86 97 L1 AND INFECTION?

=> **s l86 and review/dt**
1734424 REVIEW/DT
L87 15 L86 AND REVIEW/DT

=> **d l87, ibib abs, 1-15**

L87 ANSWER 1 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN
Full Text | Citing References
ACCESSION NUMBER: 2003:749514 HCAPLUS
DOCUMENT NUMBER: 140:104275
TITLE: Cyclooxygenase-2 inhibition and gastric cancer
AUTHOR(S): Jiang, Xiao Hua; Wong, Benjamin C. Y.
CORPORATE SOURCE: Department of Medicine, University of Hong Kong, Hong Kong, Peop. Rep. China
SOURCE: Current Pharmaceutical Design (2003), 9(27), 2281-2288
CODEN: CPDEFP; ISSN: 1381-6128
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. Epidemiol. evidences suggest that chronic use of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) might be assocd. with a reduced risk of gastrointestinal cancers, including gastric cancer. The pre-cancerous gastric lesions and gastric cancers over-expressed cyclooxygenase (COX)-2. This overexpression not only is assocd. with Helicobacter pylori **infection**, but also may be due to exposure to carcinogens. Targeted inhibition of COX, esp. the COX-2 isoform, can lead to growth inhibition and apoptosis of gastric cancer in vitro. Various mechanisms, including COX-dependent and COX-independent pathways, have been identified and will be discussed in this article. Animal xenograft models have confirmed the tumor suppressing effects of **COX-2 inhibitors**. Human studies are underway to examine the use of **COX-2 inhibitor** in the treatment of pre-cancerous lesions. **COX-2 inhibitors** have a promising role in the prevention and treatment of gastric cancer.
REFERENCE COUNT: 108 THERE ARE 108 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 2 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN
Full Text | Citing References
ACCESSION NUMBER: 2003:749509 HCAPLUS
DOCUMENT NUMBER: 140:104272
TITLE: **COX-2 inhibition**, H. pylori **infection** and the

risk of gastrointestinal complications
AUTHOR(S): Chan, Francis K. L.
CORPORATE SOURCE: Department of Medicine & Therapeutics, Prince of Wales Hospital, Hong Kong, Peop. Rep. China
SOURCE: Current Pharmaceutical Design (2003), 9(27), 2213-2219
CODEN: CPDEFP; ISSN: 1381-6128
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. Current data on the gastric safety of cyclooxygenase-2 (**COX-2**) **inhibitors** in the presence of H. pylori **infection** are largely derived from animal expts. and indirect clin. evidence. In animal models of H. pylori gastritis, **COX-2 inhibitors** suppressed prostaglandin synthesis and aggravated mucosal damage. In the human stomach, COX-1 appears to be the predominant source of prostaglandins despite the fact that COX-2 is upregulated in H. pylori gastritis. There are conflicting data on whether H. pylori alters the risk of ulcer in patients receiving **COX-2 inhibitors**. Among patients with H. pylori **infection**, rofecoxib reduced the risk of complicated gastric but not duodenal ulcers as compared to naproxen. The advantage of rofecoxib over naproxen also disappeared in patients with H. pylori **infection** and prior upper gastrointestinal events. In contrast, pooled data suggested that H. pylori increases the risk of ulcer in patients receiving nonselective nonsteroidal anti-inflammatory drugs but not in patients receiving celecoxib. In rodent gastric ulcers, COX-2 was upregulated in the granulation tissue and ulcer margin. Inhibition of COX-2 delayed healing of exptl. gastric ulcer. Limited data showed that COX-2 expression was also increased in human gastric ulcer regardless of the H. pylori status. The functional significance of COX-2 in human gastric ulcer is unknown.
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 3 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:743775 HCAPLUS
DOCUMENT NUMBER: 140:138450
TITLE: Assessment of non-steroidal anti-inflammatory drug (NSAID) damage in the human gastrointestinal tract
AUTHOR(S): James, Martin W.; Hawkey, Christopher J.
CORPORATE SOURCE: Wolfson Digestive Diseases Centre, University Hospital Nottingham, Nottingham, NG7 2UH, UK
SOURCE: British Journal of Clinical Pharmacology (2003), 56(2), 146-155
CODEN: BCPHBM; ISSN: 0306-5251
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. Aspirin is widely prescribed and confers considerable benefit to patients by reducing cardiovascular and cerebrovascular morbidity and mortality. Non-steroidal antiinflammatory drugs (NSAIDs) are effective analgesics, antipyretics and reduce the inflammatory component in conditions such as rheumatoid arthritis. However, both agents are assocd. with an increased risk of gastrointestinal symptoms and the potentially serious consequences of gastroduodenal ulceration, bleeding and perforation. The introduction of highly selective cyclooxygenase (**COX**)-**2 inhibitors** or the co-prescription gastroprotective agents with nonselective NSAIDs have offered strategies to reduce the incidence of such events. This review article analyzes the quant. techniques that can be employed by clin. pharmacologists and the clin. studies performed

to assess NSAID damage in the gastrointestinal tract.
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 4 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:109135 HCAPLUS
DOCUMENT NUMBER: 139:46185
TITLE: Chemoprevention of Helicobacter pylori-associated gastric carcinogenesis in a mouse model; is it possible?
AUTHOR(S): Hahm, Ki Baik; Song, Young Joon; Oh, Tae Young; Lee, Jeong Sang; Surh, Young-Joon; Kim, Young Bae; Yoo, Byung Moo; Kim, Jin Hong; Han, Sang Uk; Nahm, Ki Taik; Kim, Myung-Wook; Kim, Dae Yong; Cho, Sung Won
CORPORATE SOURCE: Genomic Research Center for Gastroenterology, Ajou Helicobacter Research Group, Ajou University School of Medicine, Suwon, S. Korea
SOURCE: Journal of Biochemistry and Molecular Biology (2003), 36(1), 82-94
CODEN: JBMBE5; ISSN: 1225-8687
PUBLISHER: Biochemical Society of the Republic of Korea
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Although debates still exist whether Helicobacter pylori **infection** is really class I carcinogen or not, H. pylori has been known to provoke precancerous lesions like gastric adenoma and chronic atrophic gastritis with intestinal metaplasia as well as gastric cancer. Chronic persistent, uncontrolled gastric inflammations are possible basis for ensuing gastric carcinogenesis and H. pylori **infection** increased COX-2 expressions, which might be the one of the mechanisms leading to gastric cancer. To know the implication of long-term treatment of antiinflammatory drugs, rebamipide or nimesulide, on H. pylori-assocd. gastric carcinogenesis, we infected C57BL/6 mice with H. pylori, esp. after MNU administration to promote carcinogenesis and the effects of the long-term administration of rebamipide or nimesulide were evaluated. C57BL/6 mice were sacrificed 50 wk after H. pylori **infection**. Colonization rates of H. pylori, degree of gastric inflammation and other pathol. changes including atrophic gastritis and metaplasia, serum levels and mRNA transcripts of various mouse cytokines and chemokines, and NF-κB binding activities, and finally the presence of gastric adenocarcinoma were compared between H. pylori infected group (HP), and H. pylori infected group administered with long-term rebamipide contg. pellet diets (HPR) or nimesulide mixed pellets (HPN). Gastric mucosal expressions of ICAM-1, HCAM, MMP, and transcriptional regulations of NF-κB binding were all significantly decreased in HPR group than in HP group. Multi-probe RNase protection assay showed the significantly decreased mRNA levels of apoptosis related genes and various cytokines genes like IFN-γ, RANTES, TNF-α, TNFR p75, IL-1β in HPR group. In the expt. designed to provoke gastric cancer through MNU treatment with H. pylori **infection**, the incidence of gastric carcinoma was not changed between HP and HPR group, but significantly decreased in HPN group, suggesting the chemoprevention of H. pylori-assocd. gastric carcinogenesis by **COX-2 inhibition**. Long-term administration of antiinflammatory drugs should be considered in the treatment of H. pylori since they showed the mol. and biol. advantages with possible chemopreventive effect against H. pylori-assocd. gastric carcinogenesis. If the final concrete proof showing the causal relationship between H.

pylori **infection** and gastric carcinogenesis could be obtained, that will shed new light on chemoprevention of gastric cancer, i.e., that gastric cancer could be prevented through either the eradication of H. pylori or lessening the inflammation provoked by H. pylori **infection** in high risk group.

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 5 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:400504 HCAPLUS
DOCUMENT NUMBER: 137:230031
TITLE: Cyclooxygenase-2 expression in early gastric cancer, intestinal metaplasia and Helicobacter pylori **infection**
AUTHOR(S): Walker, Marjorie M.
CORPORATE SOURCE: Imperial College School of Science, Technology and Medicine, London, W2 1PG, UK
SOURCE: European Journal of Gastroenterology & Hepatology (2002), 14(4), 347-349
CODEN: EJGHES; ISSN: 0954-691X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Cyclooxygenase (COX) is the crucial enzyme for synthesis of prostaglandins and occurs in two isoforms COX-1 and COX-2. While COX-1 is constantly expressed in the gastrointestinal tract in large quantities and probably maintains mucosal integrity through const. generation of prostaglandins, COX-2 is induced principally during inflammation. In early gastric cancer and in intestinal metaplasia the expression of COX-2 in patients infected by Helicobacter pylori is increased in intestinal type compared to diffuse type gastric cancer and in intestinal metaplasia. In tumors of mixed type, COX-2 is also increased in the intestinal component compared to the diffuse component. While there has been success of **COX-2 inhibition** for chemoprevention in colon cancer, a similar role in gastric cancer needs to be carefully assessed in the light of reported adverse effects and whether the precancerous condition, intestinal metaplasia, can truly regress.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 6 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:336003 HCAPLUS
DOCUMENT NUMBER: 137:103262
TITLE: Gastrointestinal safety of selective **COX-2 inhibitors**
AUTHOR(S): Hawkey, C. J.; Skelly, M. M.
CORPORATE SOURCE: Division of Gastroenterology, Queen's Medical Centre, University Hospital Nottingham, Nottingham, UK
SOURCE: Current Pharmaceutical Design (2002), 8(12), 1077-1089
CODEN: CPDEFP; ISSN: 1381-6128
PUBLISHER: Bentham Science Publishers
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. It appears that selective **Cox-2 inhibitors** do not affect the gastro-duodenal mucosa while having anti-inflammatory and analgesic efficacy similar to non-selective NSAIDs. Two broad categories of drugs are COX-2 selective: coxibs and a no. of pre-existing NSAIDs

retrospectively found to have selectivity. **COX-2 inhibitors** cause less dyspepsia than NSAIDs. They spare gastrointestinal mucosal generation of prostaglandins (PGs) and PG-dependant bicarbonate secretion. Coxibs cause no acute mucosal injury in endoscopic studies and serendipitous **Cox-2 inhibitors** generally cause less acute injury than non -selective NSAIDs or placebo. Both celecoxib and rofecoxib have been assocd. with a substantial redn. in endoscopic ulcers compared to NSAID comparators. In the VIGOR study all upper GI events were reduced from 4.5 per 100 patient years to 2.1 per 100 patient years with supra-therapeutic doses of rofecoxib compared with naproxen. In the CLASS study, over a period of 3 days to 6 mo, incidence of ulcer complications was 0.76% with celecoxib and 1.45% for ibuprofen or diclofenac. The less substantial redn. in events in the CLASS study compared with the VIGOR may be due, at least in part, to the fact that 21% of the patients were also on low dose aspirin. However it is premature to say that the benefit of **Cox-2 inhibitors** is lost in patients taking aspirin. There is continuing debate on the role of **Cox-2 inhibitors** in patients who have other risk factors for complicated ulcer disease e.g. patients who are elderly, on aspirin or corticosteroids, have a previous ulcer or have H. pylori **infection**.

REFERENCE COUNT: 95 THERE ARE 95 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 7 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:266581 HCAPLUS
DOCUMENT NUMBER: 137:18339
TITLE: Virus self-improvement through inflammation: No pain, no gain
AUTHOR(S): Mocarski, Edward S., Jr.
CORPORATE SOURCE: Department of Microbiology and Immunology, Stanford University School of Medicine, Stanford, CA, 94305-5124, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2002), 99(6), 3362-3364
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. The title research of H. Zhu, et al. (2002) is reviewed with commentary and refs. The study of Zhu et al. showed that prostaglandin (PG) E2, a key mediator in the inflammatory response, is induced and performs an important function to support viral replication. The study also showed that PG synthesis follows induction of cyclooxygenase-2 (COX-2) and cytoplasmic phospholipase A2 transcriptional activation during cytomegalovirus (CMV) **infection**. COX-2 is the crit. site of action for anti-inflammatory drugs like aspirin, indomethacin, and other nonsteroidal antiinflammatory drugs, as well as for a growing list of specific **COX-2 inhibitors** like celecoxib and rofecoxib.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 8 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:16664 HCAPLUS
DOCUMENT NUMBER: 136:240947
TITLE: Helicobacter pylori **infection** and the use of NSAIDs
AUTHOR(S): Bazzoli, Franco; De Luca, Luca; Graham, David Y.

CORPORATE SOURCE: Department of Internal Medicine and Gastroenterology, University of Bologna, Policlinico S. Orsola, Italy
SOURCE: Best Practice & Research, Clinical Gastroenterology (2001), 15(5), 775-785
CODEN: BPRCB6
PUBLISHER: Bailliere Tindall
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Helicobacter pylori **infection** and the use of non-steroidal anti-inflammatory drugs (NSAIDs) can each result in gastroduodenal ulcers and ulcer complications. Recent studies have suggested that there is an interaction between the two causes such that elimination of H. pylori before NSAID treatment decreases the occurrence of ulcers. This led to the conclusion of the Maastricht 2000 meeting that H. pylori eradication should be considered before embarking on long-term NSAID therapy. One of the main sources of confusion is related to the fact that prospective endoscopic studies testing various drugs for prevention of NSAID ulcers among chronic NSAID users are probably not directly applicable to problems of clin. ulcers and of ulcer complications. It has become clear that, to be interpretable clin., such studies must provide sep. analyses based on H. pylori status, history of ulcer, or an ulcer complication. Overall, the data strongly support the notion that eradication therapy is beneficial for primary prophylaxis. In contrast, one would expect little benefit when NSAIDs caused the clin. ulcer (secondary prevention) and, at best, H. pylori eradication has a modest effect on the prevention of recurrent ulcer bleeding in NSAID users who have suffered ulcer complications. The data support the notion that H. pylori eradication therapy should be given to all H. pylori-infected patients with peptic ulcers irresp. of whether or not they have used NSAIDs. Proton pump inhibitors are superior to placebo for the prevention of ulcer recurrence but are inferior to full-dose misoprostol for the prevention of ulcers among those with NSAID ulcers and no H. pylori **infection**. Selective **COX-2 inhibitors** appear to reduce markedly, but not eliminate, ulcer complications among chronic NSAID users.

REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 9 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:219377 HCAPLUS
DOCUMENT NUMBER: 135:174506
TITLE: **COX-2 inhibitors** vs. NSAIDs in gastrointestinal damage and prevention
AUTHOR(S): Ballinger, Anne; Smith, Geoff
CORPORATE SOURCE: St Bartholomew's and The Royal London School of Medicine and Dentistry, London, UK
SOURCE: Expert Opinion on Pharmacotherapy (2001), 2(1), 31-40
CODEN: EOPHF7; ISSN: 1465-6566
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 60 refs. Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit prodn. of protective gastric mucosal prostaglandins and also have a direct topical irritant effect. In some patients this results in dyspepsia and development of gastroduodenal erosions and ulceration. The risk of ulcer complications, such as bleeding, perforation and death is increased approx. 4-fold in NSAID users. Patients at high risk of ulcer complications include the elderly, those taking anticoagulants, steroids and aspirin, those with a previous history of peptic ulceration and

patients with concomitant serious medical problems. The interaction of NSAIDs with Helicobacter pylori (the major cause of peptic ulceration in non-NSAID users) is controversial and some studies suggest that H. pylori **infection** may even protect against NSAID-induced ulceration. Selective inhibitors of the inducible cyclooxygenase-2 (COX-2) enzyme spare COX-1 in the gastric mucosa and, hence, do not inhibit prodn. of mucosal prostaglandins. COX-2-selective inhibitors are assocd. with a significant redn. in gastroduodenal damage compared with traditional NSAIDs. Proton pump inhibitors (PPI) are probably the best agents for healing and prevention of NSAID-induced ulcers. Preliminary studies suggest that COX-2 selective inhibitors, like traditional NSAIDs, may prevent lower gastrointestinal cancer. Further studies are needed but they may be useful in individuals at high risk of certain types of lower gastrointestinal malignancy with increased gastrointestinal tolerability and safety.

REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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Full Text | Citing References

ACCESSION NUMBER: 2000:476597 HCAPLUS
DOCUMENT NUMBER: 133:171627
TITLE: Novel therapeutic approaches to gastric and duodenal ulcers: an update
AUTHOR(S): Dajani, Esam Z.; Klamut, Michael J.
CORPORATE SOURCE: Long Grove, Illinois and Gastroenterology Section, Loyola University Medical Center, International Drug Development Consultants Corporation, Chicago, IL, USA
SOURCE: Expert Opinion on Investigational Drugs (2000), 9(7), 1537-1544
CODEN: EOIDER; ISSN: 1354-3784
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 53 refs. Over the last 25 yr, a remarkable revolution in the pathophysiol. and treatment of gastric and duodenal ulcers has occurred. Effective therapies were developed not only to heal ulcers, but also to cure most patients. The two principal causes for gastric and duodenal ulcers are either **infection** with Helicobacter pylori or the use of non-steroidal anti-inflammatory drugs (NSAIDs). With H. pylori eradication, gastric and duodenal ulcers are rapidly becoming historical diseases. This communication reviews the salient pharmacol. of the novel anti-ulcer drugs currently in development, with particular emphasis on the treatment of gastric and duodenal ulcers. Intense research is currently focused on the development of proton pump inhibitors primarily for the treatment and prevention of gastroesophageal reflux disease. The older proton pump inhibitors, omeprazole and lansoprazole, are effective in healing gastric and duodenal ulcers. Furthermore, both drugs are effective in eradicating H. pylori when given with various antibiotics. Pantoprazole, rabeprazole and esomeprazole are new proton pump inhibitors, which appear to have comparable therapeutic profiles with omeprazole and lansoprazole. Rebamipide is a new mucosal protective drug, which is effective in healing gastric ulcers. Polaprezinc and nocloprost are also mucosal protective drugs, which are in clin. development. However, none of these three cytoprotective drugs have been evaluated for their efficacy in eradicating H. pylori when given in combination with antibiotics. Likewise, no published literature exists on the use of these drugs for preventing NSAID-induced ulcers. With the rapid eradication of H. pylori currently happening in the developed world, the therapeutic challenge is

now directed toward preventing NSAID-assocd. ulcer. Significant redn. of NSAID-induced ulcers is achieved by using continuous prophylactic anti-ulcer therapy (misoprostol or omeprazole) or by using NSAIDs possessing selective **COX-2 inhibitory** activity. However, outcome clin. studies are needed to compare the adjuvant anti-ulcer therapies given with COX-1 inhibitors vs. the selective **COX-2 inhibitors** given alone.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 11 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2000:264220 HCAPLUS
DOCUMENT NUMBER: 133:175280
TITLE: Apoptosis in the gastric mucosa: molecular mechanisms, basic and clinical implications
AUTHOR(S): Szabo, I.; Tarnawski, A. S.
CORPORATE SOURCE: Medical Service, Department of Veterans Affairs Medical Center, Long Beach, Department of Medicine, University of California, Irvine, CA, USA
SOURCE: Journal of Physiology and Pharmacology (2000), 51(1), 3-15
CODEN: JPHPEI; ISSN: 0867-5910
PUBLISHER: Polish Physiological Society
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review, with 71 refs. Apoptosis a programmed cell death, is an essential mechanism of eliminating damaged or aged cells and thus to maintain tissue integrity. There are two central pathways that lead to apoptosis: a) the pos. induction by ligands (death factors) binding to plasma membrane receptors (death factor receptors) and b) neg. induction by the loss of suppressor activity. The common execution mechanisms of apoptosis consist of the activation of cytosolic aspartate-specific proteases (ICE-proteases) termed caspases, which can be activated via various intracellular pathways. In the stomach, mucosal surface epithelial cells are constantly exfoliating to the gastric lumen and completely replaced within 3-5 days under physiol. conditions. Apoptosis has been reported to take place in all regions of the stomach with apoptotic cells occurring predominantly in the superficial parts of the gastric glands, at a rate of 2-3% for all cells. Following mucosal injury (e.g. ulcer development), apoptosis rapidly increases and remains elevated for 2-3 mo. In a 3-mo old ulcer scar, the apoptosis rate of mucous, parietal, chief and endocrine cells was found to be similar to that of normal gastric mucosa. Helicobacter pylori (H. pylori) **infection** induces apoptosis in the gastric mucosa and this action appears to be independent of VacA cytotoxin of H. pylori strains. Nonsteroidal anti-inflammatory drugs (NSAIDs), esp. cyclooxygenase-2 (**COX-2**) **inhibitors** are potent inductors of gastric epithelial cell apoptosis. However, they can abrogate apoptosis or proliferation effects induced by H. pylori. Many details of the exact intracellular and mol. mechanisms regulating apoptosis in gastric mucosa remain to be elucidated.

REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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Full Text | Citing References

ACCESSION NUMBER: 2000:75849 HCAPLUS
DOCUMENT NUMBER: 133:37

TITLE: Do cyclooxygenase-2 inhibitors provide benefits similar to those of traditional nonsteroidal anti-inflammatory drugs, with less gastrointestinal toxicity?
AUTHOR(S): Feldman, Mark; McMahon, Alexander T.
CORPORATE SOURCE: Dallas Veterans Affairs Medical Center, Dallas, TX, 75216, USA
SOURCE: Annals of Internal Medicine (2000), 132(2), 134-143
CODEN: AIMEAS; ISSN: 0003-4819
PUBLISHER: American College of Physicians-American Society of Internal Medicine
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review and discussion with 73 refs. Two forms of cyclooxygenase, cyclooxygenase-1 (COX-1) and cyclooxygenase 2 (COX-2), act as rate-limiting enzymes in prostaglandin and thromboxane synthesis. Discovery of these compds. led to the development of drugs that selectively or specifically inhibit the COX-2 isoform. Although the COX-1 isoform is expressed at fairly const. levels in cells, including the gastrointestinal mucosa and platelets, expression of COX-2 varies greatly. In many cells, low expression of COX-2 can be upregulated by various stimuli, including inflammatory cytokines, bacterial toxins, and growth factors; this suggests that COX-2 plays a role in inflammation, **infection**, and cellular proliferation. It was thought that newly developed drugs designed to block COX-2 but not COX-1 would have anti-inflammatory properties and would avoid inhibiting the synthesis of gastrointestinal prostaglandins (thereby avoiding ulcers) and platelet thromboxane (thereby avoiding bleeding). Gastrointestinal ulcers and bleeding are side effects of traditional nonsteroidal anti-inflammatory drugs (NSAIDs) that block COX-1 and COX-2. Meloxicam and nimesulide, selective **COX-2 inhibitors** available outside the United States, are as effective as traditional NSAIDs but have similar gastrointestinal side effects. Celecoxib (Celebrex, G.D. Searle and Co., Chicago, Illinois) and rofecoxib (Vioxx, Merck and Co., Inc., West Point, Pennsylvania), selective **COX-2 inhibitors** approved in the United States in the past year, are also as effective as traditional NSAIDs. However, celecoxib and rofecoxib have no antiplatelet activity and lead to fewer endoscopically detected gastric and duodenal ulcers than traditional NSAIDs, such as ibuprofen or naproxen. Preliminary analyses of data pooled from several trials suggest that celecoxib and rofecoxib are assocd. with fewer clin. symptomatic ulcers and ulcer complications than traditional NSAIDs are. Postmarketing surveillance should help clarify the actual risk for serious ulcer complications with these new **COX-2 inhibitors** and reveal other potential nongastrointestinal toxic reactions that can result from their use.

REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 13 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1999:276770 HCAPLUS
DOCUMENT NUMBER: 130:320289
TITLE: Specific **COX-2 inhibitors** in arthritis, oncology, and beyond: where is the science headed?
AUTHOR(S): Lipsky, Peter E.
CORPORATE SOURCE: The University of Texas Southwestern Medical Center at Dallas, Dallas, TX, 75235-8884, USA
SOURCE: Journal of Rheumatology, Supplement (1999), 56(Arthritis into the Next Millennium), 25-30

CODEN: JRSUDX; ISSN: 0380-0903
PUBLISHER: Journal of Rheumatology Publishing Co. Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 88 refs. The existence of two distinct isoforms of cyclooxygenase (COX), which convert arachidonic acid to prostanoids, is now well established. COX-1, which is constitutively expressed in many tissues (including the gastrointestinal tract, platelets, and kidney) is responsible for producing prostanoids that regulate normal housekeeping or physiol. functions. In contrast, COX-2 is the inducible form responsible for the prodn. of prostanoids in response to a variety of evoking stimuli in different tissues and for mediation of inflammation and pain in certain diseases. Since the identification of COX-2, a great deal of research has been devoted to elucidating and understanding its mol. and physiol. characteristics. As a result of research into the differences between COX-1 and COX-2, new insights into the role of each isoform in normal homeostasis and in their responses to exogenous stimuli have emerged. Besides its induction in cells at inflammatory sites, COX-2 is known to be induced in the kidney in response to sodium depletion or in hyperfiltration states; in postsynaptic excitatory neurons in the brain after electroconvulsive stimulation; in the ovary and uterus during ovulation and implantation; in intestinal epithelium after bacterial **infection**; as well as in colon adenoma and carcinoma cells. These findings, largely from animal studies, have suggested a broader spectrum of biol. activity of COX-2 and potential alterations of specific physiol. or protective mechanisms by inhibition of COX-2, as well as potential new clin. targets of therapy with **COX-2 inhibitors**. As COX-2 appears to play an important role in pathol. processes other than pain and inflammation, ongoing research is investigating the potential utility of **COX-2 inhibitors** in other conditions, such as colonic polyposis, colorectal cancer, and Alzheimer's disease.

REFERENCE COUNT: 88 THERE ARE 88 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 14 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1998:404547 HCAPLUS
DOCUMENT NUMBER: 129:173761
TITLE: COX-2, TNF-α and apoptosis: newer strategies in inflammatory disorders
AUTHOR(S): Kulkarni, S. K.; Varghese, Navin P.
CORPORATE SOURCE: Pharmacology Division, University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, 160 014, India
SOURCE: Indian Drugs (1998), 35(5), 245-260
CODEN: INDRBA; ISSN: 0019-462X
PUBLISHER: Indian Drug Manufacturers' Association
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review, with 73 refs. Inflammatory conditions related to rheumatoid arthritis, injury and **infection** necessitates the need for the use of nonsteroidal antiinflammatory drugs (NSAIDs) to curb these ailments. There have been high levels of concern regarding their use since extensive and indiscriminate use of NSAIDs results in toxicity. The need for an overall therapeutic benefit with no or reduced toxicity has envisaged the need for investigating newer sites of antiinflammatory activity. This article highlights the development of selective **COX-2 inhibitors**, and newer concepts of antiTNF-α therapy and induction of apoptosis as potential strategies in combating inflammation.

REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L87 ANSWER 15 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1997:408803 HCAPLUS
DOCUMENT NUMBER: 127:75383
TITLE: Recent clinical trials in the rheumatic diseases
AUTHOR(S): Matteson, Eric L.
CORPORATE SOURCE: Division of Rheumatology, Department of Internal Medicine, Mayo Clinic and Graduate School of Medicine, Rochester, MN, 55905, USA
SOURCE: Current Opinion in Rheumatology (1997), 9(2), 95-101
CODEN: CORHES; ISSN: 1040-8711
PUBLISHER: Rapid Science Publishers
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB This paper reviews with 49 refs. clin. trials that have been published during the course of the past year on the rheumatol. diseases. The greatest no. of clin. trials were done in rheumatoid arthritis. These trials show promising results for combination therapy with disease-modifying antirheumatic drugs, whereas results of studies with monoclonal antilymphocyte antibodies have been disappointing. The role of oral collagen remains to be defined. Nonsteroidal anti-inflammatory drugs with selective cyclooxygenase-2 (**Cox-2**) **inhibition** may have a more favorable toxicity profile and are likely to find wide use. As adjuvant therapy, trimethoprim-sulfamethoxazole appears to be useful in preventing relapses in Wegener's granulomatosis, and patients develop fewer **infections**. With the exception of juvenile rheumatoid arthritis, i.v. Ig therapy appeared ineffective in the diseases studied. The inclusion of more standardized and disease-specific outcome measures has enhanced the quality of clin. trials in rheumatol. and their applicability to rheumatol. practice.

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=> s l1 and metabolism?
        541558 METABOLISM?
        418336 METAB
           699 METABS
        418667 METAB
                  (METAB OR METABS)
        760734 METABOLISM?
                  (METABOLISM? OR METAB)
L88          86 L1 AND METABOLISM?

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       1734424 REVIEW/DT
L89          24 L88 AND REVIEW/DT

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L89 ANSWER 1 OF 24 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2004:75409 HCAPLUS
DOCUMENT NUMBER: 140:250985
TITLE: Cyclooxygenase-2 Expression and Inhibition in Atherothrombosis
AUTHOR(S): Cipollone, Francesco; Rocca, Bianca; Patrono, Carlo

CORPORATE SOURCE: Center of Excellence on Aging, "G. D'Annunzio" University of Chieti School of Medicine, Chieti, Italy
SOURCE: Arteriosclerosis, Thrombosis, and Vascular Biology (2004), 24(2), 246-255
CODEN: ATVBFA; ISSN: 1079-5642
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Arachidonic acid **metab**. plays an important role in acute ischemic syndromes affecting the coronary or cerebrovascular territory, as reflected by biochem. measurements of eicosanoid biosynthesis and the results of inhibitor trials in these settings. Two cyclooxygenase (COX)-isoenzymes have been characterized, COX-1 and COX-2, that differ in terms of regulatory mechanisms of expression, tissue distribution, substrate specificity, preferential coupling to upstream and downstream enzymes, and susceptibility to inhibition by the extremely heterogeneous class of COX-inhibitors. Although the role of platelet COX-1 in acute coronary syndromes and ischemic stroke is firmly established through ≈20 yr of thromboxane metabolite measurements and aspirin trials, the role of COX-2 expression and inhibition in atherothrombosis is substantially uncertain, because the enzyme was first characterized in 1991 and selective **COX-2 inhibitors** became com. available only in 1998. In this review, we discuss the pattern of expression of COX-2 in the cellular players of atherothrombosis, its role as a determinant of plaque "vulnerability," and the clin. consequences of **COX-2 inhibition**. Recent studies from our group suggest that variable expression of upstream and downstream enzymes in the prostanoid biosynthetic cascade may represent important determinants of the functional consequences of COX-2 expression and inhibition in different clin. settings.

REFERENCE COUNT: 115 THERE ARE 115 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L89 ANSWER 2 OF 24 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:1009161 HCAPLUS
DOCUMENT NUMBER: 140:367885
TITLE: The role of cyclooxygenase-2 inhibition for the prevention and treatment of prostate carcinoma
AUTHOR(S): Lin, Daniel W.; Nelson, Peter S.
CORPORATE SOURCE: Department of Urology, Fred Hutchinson Cancer Research Center, Seattle, USA
SOURCE: Clinical Prostate Cancer (2003), 2(2), 119-126
CODEN: CPCLC4; ISSN: 1540-0352
PUBLISHER: Cancer Information Group
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Exptl. and epidemiol. studies have demonstrated that non-steroidal antiinflammatory drugs (NSAIDs) are effective in the prevention of human cancers. Nonsteroidal antiinflammatory drugs inhibit the cyclooxygenase (COX) enzyme that functions to convert arachidonic acid to prostaglandins (PGs). Cyclooxygenase-2, a key COX isoenzyme, is rapidly induced in response to inflammatory stimuli, growth factors, cytokines, and promoters of neoplastic growth. Cyclooxygenase-2-catalyzed reactions may be involved in carcinogenesis via 2 distinct mechanisms: (1) DNA damage and (2) PG-mediated effects. Reactions mediated by COX-2 form reactive oxygen species that can directly induce the oxidn. of DNA or instigate the bioactivation of carcinogens. Prostaglandin E2, a byproduct

of COX-2-mediated arachidonic acid **metab**., exhibits several biol. actions that have been shown to promote tumorigenesis and tumor progression. These actions include increased cell proliferation, promotion of angiogenesis, and the elevated expression of the antiapoptotic protein Bcl-2. In addn., PGE2 decreases natural killer cell activity and alters immune surveillance. In vitro exptl. studies find that **COX-2 inhibitors** decrease cellular proliferation, increase apoptosis, and modulate genes involved in cell cycle regulation. Evidence from animal studies supports a role for NSAIDs in prostate cancer (CaP) prevention. Population-based studies have obsd. a reduced incidence of CaP among men using NSAIDs. Because CaP evolves slowly and rarely strikes men before the sixth or seventh decade of life, any strategy to delay or lengthen the time to development of clin. evident CaP, such as chemoprevention strategies, would greatly impact the natural history of this disease. Recent progress and crit. analyses in the roles of **COX-2 inhibition** on prostate carcinogenesis and CaP prevention will be presented.

REFERENCE COUNT: 103 THERE ARE 103 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L89 ANSWER 3 OF 24 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:903533 HCAPLUS
DOCUMENT NUMBER: 140:209710
TITLE: Breast cancer prevention-clinical trials strategies involving aromatase inhibitors
AUTHOR(S): Goss, Paul E.
CORPORATE SOURCE: Princess Margaret Hospital, University Health Network, Breast Cancer Prevention Program, University of Toronto, Toronto, ON, M5G 2M9, Can.
SOURCE: Journal of Steroid Biochemistry and Molecular Biology (2003), 86(3-5), 487-493
CODEN: JSBBEZ; ISSN: 0960-0760
PUBLISHER: : Elsevier Science Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Estrogens and their metabolites have been implicated in both the initiation and the prevention of breast cancer. The redn. in breast cancer incidence seen in the tamoxifen arms of the four prospective trials to date has established the proof of principle that antagonizing estrogen is a potential means of reducing breast cancer risk. However, the areas to improve on these results include: (a) enhanced efficacy, (b) redn. in the incidence of receptor-neg. tumors, (c) improved overall and endocrinol. side effects, and (d) improved function on end-organs other than the breast. The aromatase inhibitors offer the potential to achieve these goals in part in the following ways: (a) greater redn. in risk of disease as evidenced by superior efficacy in advanced breast cancer and by inhibition of both initiation and promotion of breast cancer, (b) redn. in receptor-neg. tumors by synergy with **COX-2 inhibitors** resulting in growth factor inhibition, anti-angiogenesis and inhibition of tumor-assocd. aromatase expression, (c) fewer vasomotor and urogenital abnormalities, and (d) reduced thromboembolism and cardiovascular complications and satisfactory effects on bone **metab**. Important differences may exist between non-steroidal reversible inhibitors and steroidal irreversible inactivators in particular related to the androgenic/anabolic effects of the steroidal inactivators. Pilot studies of aromatase inhibitors described elsewhere in this session have begun in healthy women with dense mammog., or a high-risk genetic and/or

histocytopathol. profile, to det. potential efficacy, as well as effects on end-organ function. A no. of phase three trials with aromatase inhibitors are also underway or in planning. Among these are the BRCA 1 and 2 study of exemestane vs. placebo in unaffected postmenopausal carriers, the International Breast Intervention Study 2 (IBIS 2) of anastrozole vs. placebo in women with a high-risk profile, and the National Cancer Institute of Canada's Clin. Trial Group (NCIC CTG) study of exemestane with or without celecoxib vs. placebo in women at risk of the disease. For premenopausal women, combination strategies of gonadotrophin agonists and aromatase inhibitors are being investigated. The potential of using low doses of aromatase inhibitors to lower "in breast" estrogen levels without unduly perturbing plasma concns. is also being explored. The potential of the aromatase gene functioning as an oncogene within the breast may be tied to breast d. which in turn may represent both a selection tool for elevated risk and an intermediate marker of prevention. The strong link between postmenopausal estrogen levels and breast cancer risk suggests the possibility that plasma estrogen levels may be a useful intermediate marker of prevention. The aromatase inhibitors offer us the first ever tool to render women virtually free of estrogen and are potentially an exciting tool for the prevention of breast cancer.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L89 ANSWER 4 OF 24 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:605586 HCAPLUS
DOCUMENT NUMBER: 140:35160
TITLE: Pharmacokinetics of rofecoxib: A specific cyclo-oxygenase-2 inhibitor
AUTHOR(S): Davies, Neal M.; Teng, Xiao W.; Skjodt, Neil M.
CORPORATE SOURCE: Department of Pharmaceutical Sciences, College of Pharmacy, Washington State University, Pullman, WA, USA
SOURCE: Clinical Pharmacokinetics (2003), 42(6), 545-556
CODEN: CPKNDH; ISSN: 0312-5963
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Rofecoxib is a commonly used specific cyclo-oxygenase-2 (**COX-2**) **inhibitor**. Rofecoxib has high bioavailability, poor aq. soly., an elimination half-life suitable for daily administration and a vol. of distribution approximating body mass. Species-specific, predominantly hepatic, **metab**. occurs, with novel enterohepatic circulation in rats and O-glucuronidation by uridine diphosphate-glucuronosyl transferase (UGT) 2B7 and 2B15 in human liver microsomes. Discrepancies in studies of postoperative analgesia can be putatively explained by known pharmacokinetics. Changes in rofecoxib disposition and pharmacokinetics are evident between races, in elderly patients, in patients with chronic renal insufficiency and in patients with mild to moderate hepatic impairment. Despite the selective action of **COX-2 inhibitors**, there remains the potential for significant drug interactions. Rofecoxib has been shown to have interactions with rifampicin (rifampin), warfarin, lithium and angiotensin converting enzyme (ACE) inhibitors and theophylline. **COX-2 inhibitors** represent a major therapeutic advance in terms of gastrointestinal safety; however, long-term safety in other organ systems and with concomitant drug administration still remain to be proven.

REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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Full Text | Citing References

ACCESSION NUMBER: 2003:331279 HCAPLUS
DOCUMENT NUMBER: 139:34126
TITLE: Cyclooxygenases. I. Role in inflammation
AUTHOR(S): Kolaczkowska, Elzbieta
CORPORATE SOURCE: Zakl. Immunol. Ewolucyjnej, Inst. Zool., Uniw. Jagiellonski, Krakow, 30-060, Pol.
SOURCE: Postepy Biologii Komorki (2002), 29(4), 533-554
CODEN: PBKODV; ISSN: 0324-833X
PUBLISHER: Fundacja Biologii Komorki i Biologii Molekularnej
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: Polish

AB A review. Cyclooxygenases are enzymes involved in **metab**. of membrane phospholipid derivs. leading to the formation of prostanoids, such as prostaglandins and thromboxanes. Prostaglandins control different physiol. processes, such as protection of gastrointestinal integrity, renal functions, reprodn., and inflammation. Cyclooxygenase has at least 2 isoforms coded by different genes located on different chromosomes. Significant differences between the 2 isoforms are also obsd. on the mRNA level, but both enzymes have similar primary protein structures and identical catalytic activity. Cyclooxygenase-1 (COX-1) is involved in the homeostatic control of the body under normal conditions and in the early stages of inflammation. COX-2 is also involved in the resoln. of inflammation since its activity produces cyclopentenone prostaglandins of the J-series (PGD2 metabolites), such as 15-deoxy-Δ12,14PGJ2. These prostaglandins have anti-inflammatory properties as they activate the nuclear receptor PPAR-γ and/or inhibit nuclear factor NF-κB. To explain these contradictory activities of COX-2, a hypothesis was postulated that pro-inflammatory activity should be attributed to COX-2 and the anti-inflammatory properties to the third isoform of COX (COX-3). The putative COX-3 could be structurally similar to COX-2, maybe even encoded by the same gene since its activity can be blocked by selective **COX-2 inhibitors**. Implications of the COX-3 existence for the treatment of inflammatory diseases are discussed in Part II of this review article.

L89 ANSWER 6 OF 24 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:168420 HCAPLUS
DOCUMENT NUMBER: 138:335184
TITLE: Prostaglandins and cyclooxygenase: their probable role in cancer
AUTHOR(S): Rishikesh, M. K.; Sadhana, S. S.
CORPORATE SOURCE: Department of Chemical Technology, University of Mumbai (U. D. C. T.), Mumbai, 400 019, India
SOURCE: Indian Journal of Pharmacology (2003), 35(1), 3-12
CODEN: INJPD2; ISSN: 0253-7613
PUBLISHER: Indian Pharmacological Society
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Levels, of COX-2 isoenzyme and certain prostaglandins like PGE2, PGF2α and PGE1 are found, to be higher, in certain cancers like colorectal carcinoma, squamous cell carcinoma of head and neck and certain types of breast cancer. They have been shown to aid carcinogenesis by altering cell proliferation, tumor angiogenesis,

apoptosis, immunity and carcinogen **metab**. Decreasing the high levels of COX-2 and above-mentioned prostaglandins has shown to decease carcinogenesis. Cyclopentanone prostaglandins like PGJ2 and PGA1 have been, shown to have anti-tumor effects. These act directly by suppressing the oncogenes or indirectly by preventing efflux of anti-neoplastic agents from resistant cancer cells. **COX-2 inhibitors**, PGA1 and PGJ2 may be of vital importance in future cancer therapy.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L89 ANSWER 7 OF 24 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:813502 HCAPLUS
DOCUMENT NUMBER: 138:331034
TITLE: Selective cyclooxygenase-2 inhibitors and non-small cell lung cancer
AUTHOR(S): Gridelli, C.; Maione, P.; Airoma, G.; Rossi, A.
CORPORATE SOURCE: Division of Medical Oncology, "S.G. Moscati" Hospital, Avellino, 83100, Italy
SOURCE: Current Medicinal Chemistry (2002), 9(21), 1851-1858
CODEN: CMCHE7; ISSN: 0929-8673
PUBLISHER: Bentham Science Publishers
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Lung cancer is the leading cause of death from cancer in most developed nations. The most common type of lung cancer is of non-small cell histol., representing approx. 80% of the total. Despite aggressive treatments in early stages and improvement of polychemotherapy outcomes in advanced disease, the five years survival rate for lung cancer remains under 15%. Fortunately, our improved knowledge of tumor biol. and mechanisms of oncogenesis suggests several new potential targets for clin. research in cancer therapy. A substantial body of evidence indicates that cyclooxygenase (COX)-2 and prostaglandins (PGs) play an important role in tumorigenesis. Mechanisms involved in COX-2 participation in tumorigenesis and tumor growth include xenobiotic **metab**., angiogenesis stimulation, inhibition of immune surveillance and inhibition of apoptosis. COX-2 is frequently overexpressed in bronchial premalignancy, lung adenocarcinoma and squamous cell carcinoma and COX-2 overexpression is a marker of poor prognosis in surgically resected stage I non-small cell lung cancer. Treatment with **COX-2 inhibitors** reduces the growth of NSCLC cells in vitro and in xenograft studies. Recent studies have defined some of the mechanisms involved in COX-2 participation in NSCLC development and diffusion. These evidences support the hypothesis that selective **COX-2 inhibitors** (coxibs) may prove beneficial in the prevention and treatment of NSCLC.

REFERENCE COUNT: 78 THERE ARE 78 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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Full Text | Citing References

ACCESSION NUMBER: 2002:481597 HCAPLUS
DOCUMENT NUMBER: 137:379544
TITLE: Non-steroidal anti-inflammatory drugs in cancer treatment
AUTHOR(S): Cuender, Muriel; Pezzuro, John M.
CORPORATE SOURCE: Department of Medicinal chemistry and Pharmacognosy, University of Illinois at Chicago, Chicago, IL, 60612, USA

SOURCE: Expert Opinion on Therapeutic Patents (2002), 12(6), 827-835
CODEN: EOTPEG; ISSN: 1354-3776
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Epidemiol. studies have demonstrated that non-steroidal anti-inflammatory drugs (NSAIDs), which are potent cyclooxygenase (COX) inhibitors, mediate cancer preventive and tumor regressive effects in the human colon. COX is responsible for the biosynthesis of prostaglandins (PGs), represented by a large series of compds. Importantly, an increase in PG synthesis may influence tumor growth in humans or exptl. animals, and numerous studies have illustrated the effect of PG synthesis on carcinogen **metab**., tumor cell proliferation and metastatic potential. The patents discussed in this review present the synthesis and activities of some selective **COX-2 inhibitors**, the activity and toxicity of R-NSAIDs and S-NSAIDs, and some results obtained with NSAIDs combined with chemotherapeutic agents, in cancer treatment.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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Full Text | Citing References

ACCESSION NUMBER: 2002:217540 HCAPLUS
DOCUMENT NUMBER: 136:303502
TITLE: Valdecoxib: A **COX-2 inhibitor** for treatment of osteoarthritis, rheumatoid arthritis, and primary dysmenorrhea
AUTHOR(S): Goldman, Monica; Schutzer, Steven
CORPORATE SOURCE: Hartford (CT) Hospital, USA
SOURCE: Formulary (2002), 37(2), 68, 71-74, 76-77
CODEN: FORMF9; ISSN: 1082-801X
PUBLISHER: Advanstar Communications, Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Valdecoxib is a new COX-2-specific inhibitor approved for relief of signs and symptoms of osteoarthritis and adult rheumatoid arthritis and for treatment of primary dysmenorrhea. Its **COX-2 inhibitory** potency is equal to that of celecoxib. Although it provides less COX-1 enzyme inhibition than celecoxib, this may not be clin. relevant. Controlled trials have shown valdecoxib to be safe and to provide comparable efficacy to naproxen in arthritis symptom score improvement, redn. of menstruation-assocd. pain, and postoperative analgesia. Valdecoxib has an adverse effect profile similar to that of other **COX-2 inhibitors**, including a gastrointestinal safety benefit over conventional NSAIDs and minimal antiplatelet effects. The risk of reduced renal glomerular filtration rate and acute renal failure appears to be the same as with other **COX-2 inhibitors** and conventional NSAIDs. As with other NSAIDs and **COX-2 inhibitors**, most renal adverse events are a result of sodium retention, peripheral edema, and blood pressure elevation. Valdecoxib has a modest inhibitory effect on **metab**. of drugs via the cytochrome P 450 3A4, 2C9, 2C19, and 2D6 isoenzymes, but this may not be clin. relevant unless the interacting drug has a narrow therapeutic index. Valdecoxib may be a useful formulary addn. as an alternative to traditional NSAIDs for patients in whom gastrointestinal safety or bleeding is a concern.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L89 ANSWER 10 OF 24 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:136698 HCAPLUS
DOCUMENT NUMBER: 136:395185
TITLE: Non steroidal anti-inflammatory and anti-allergy agents
AUTHOR(S): Kontogiorgis, C. A.; Hadjipavlou-Litina, D. J.
CORPORATE SOURCE: Department of Pharmaceutical Chemistry, School of Pharmacy, Aristotelian University of Thessaloniki, Thessaloniki, 54006, Greece
SOURCE: Current Medicinal Chemistry (2002), 9(1), 89-98
CODEN: CMCHE7; ISSN: 0929-8673
PUBLISHER: Bentham Science Publishers
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Non steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used for inflammation therapy. The major drawback in using the NSAIDs is in their tendency to cause gastrointestinal toxicity. Since the roles of arachidonic acid (A.A) metabolites, as leukotrienes (Lts), prostaglandins (PGs) and thromboxanes (TXA2) as mediators of the inflammatory reaction were clarified, much effort has been made to develop inhibitors of the prodn. of these chem. mediators as anti-inflammatory agents. These mediators also play important roles in some inflammatory or allergic diseases, acting either alone or in combination and inhibitors of 5-lipoxygenase (5-LOX) and/or cyclooxygenase isoforms 1,2 (COX-1,2) may be useful for the treatment of asthma, psoriasis and rheumatoid arthritis. Leukotrienes, the products of 5-LOX **metab**. have been assocd. with immediate hypersensitivity reactions, anaphylaxis and asthma. In addn., active oxygen species (AOS) including superoxide anion (O2-), hydrogen peroxide, hydroxyl radical and ferric radical, mediate cell damage in a variety of pathophysiol. conditions and are responsible for oxidative injury of enzymes, lipid membranes and DNA in living cells and tissues. Prostaglandins and leukotrienes in the arachidonate pathway linked with lipid peroxidn. may amplify the oxidative damage. Nitric oxide (NO) plays also a role as an effector in inflammation, since PG and NO thought to be important in maintaining mucosal integrity. Dual or selective inhibitors, specific receptor antagonists, AOS scavengers, and NO donors have been under development for therapeutic application. Several classes of inhibitors have been identified and at least 12 major chem. series are known to affect PGs prodn. directly. In this review, we account on our research work concerning NSAIDs combined with a ref. of the recent literature.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L89 ANSWER 11 OF 24 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:921233 HCAPLUS
DOCUMENT NUMBER: 137:72356
TITLE: Pros and cons of selective inhibition of cyclooxygenase-2 versus dual lipoxygenase/cyclooxygenase inhibition: Is two better than one?
AUTHOR(S): Parente, Luca
CORPORATE SOURCE: Dep. of Pharmacology Sci., Univ. of Salerno, Fisciano(Salerno), 84084, Italy
SOURCE: Journal of Rheumatology (2001), 28(11), 2375-2382
CODEN: JRHUA9; ISSN: 0315-162X

PUBLISHER: Journal of Rheumatology Publishing Co. Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review on the two targets of drug action, cyclooxygenase-2 and 5-lipoxygenase (5-LOX), evaluating both the effects and the clin. implications of the inhibition of the single enzymes vs. the combined dual inhibition of the two enzymes. Incidence of unwanted gastrointestinal (GI) effects are reduced with the highly selective **COX-2 inhibitors** compared to classical nonspecific COX inhibitors. The prostaglandins produced by COX-2 are involved in various physiol. housekeeping functions like adaptive cytoprotection in the GI mucosa, synthesis of antiaggregatory PGI2 by endothelial cells, formation of vasodilatory PGE2 in the kidney, and regulation of the reproductive processes. In exptl. settings, dual 5-LOX/COX inhibitors are potent antiinflammatory drugs. The pharmacol. profile of dual 5-LOX/COX inhibitors is similar to that of antiinflammatory glucocorticoids, which inhibit phospholipase A2 (PLA2), and prevent arachidonic acid **metab**. by both COX and 5-LOX. Dual inhibitors do not affect intermediate **metab**. or endocrine functions, do not lead to severe side effects normally related with the use of glucocorticoids, and show protective effects on GI mucosa.
REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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Full Text | Citing References

ACCESSION NUMBER: 2001:554482 HCAPLUS
DOCUMENT NUMBER: 136:272445
TITLE: The pharmacological profile of ML3000: a new pyrrolizine derivative inhibiting the enzymes cyclo-oxygenase and 5-lipoxygenase
AUTHOR(S): Tries, S.; Laufer, S.
CORPORATE SOURCE: R&D Division, Merckle GmbH, Blaubeuren, 7, 89143, Germany
SOURCE: Inflammopharmacology (2001), 9(1-2), 113-124
CODEN: IAOAES; ISSN: 0925-4692
PUBLISHER: VSP BV
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with refs. Since the discovery of aspirin about one century ago, many non-steroidal anti-inflammatory drugs (NSAIDs) have been used for the treatment of inflammatory states and pain. While the NSAIDs are generally safe and effective, common side effects frequently limit therapy. Typical mechanism-based side effects are gastrointestinal (GI)-related, ranging from GI upset and intolerance to ulceration and bleeding after long-term therapy. In order to overcome these side effects several strategies have been followed, among them the development of selective **COX-2 inhibitors**. Our strategy to find compds. that are active on the one hand and tolerated by the GI tract on the other hand, is based on the shunt to leukotrienes. This theory is founded upon the fact that NSAIDs, while inhibiting the cyclooxygenase branch of the arachidonic acid cascade, are able to increase the 5-lipoxygenase (5-LOX) branch of arachidonic acid **metab**. This shunt to the 5-LOX side leads to the increase in chemotactic LTB4 and vasoconstrictive peptidoleukotrienes, the contributory effects of which to gastrointestinal disorders are widely accepted. Therefore, the design of anti-inflammatory compds. with 5-LOX inhibitory effects seems reasonable. With the compd. ML3000, this theory has gained further evidence. ML3000 is an anti-inflammatory compd. with potent activity in various animal expts. that represent models for acute and chronic inflammation, pain, fever and asthma. It is a balanced

inhibitor of the enzymes 5-LOX and COX-1/2 in the submicromolar range. The compd. demonstrates excellent gastrointestinal tolerance in various animal species. The preclin. profile of ML3000, which is currently in Phase III clin. development, is presented in this publication.
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L89 ANSWER 13 OF 24 HCAPLUS COPYRIGHT 2004 ACS on STN
Full Text | Citing References
ACCESSION NUMBER: 2001:554479 HCAPLUS
DOCUMENT NUMBER: 135:326831
TITLE: Clinical pharmacokinetics and **metabolism** of nimesulide
AUTHOR(S): Bernareggi, Alberto
CORPORATE SOURCE: Drug Department, Novuspharma SpA, Monza, 20052, Italy
SOURCE: Inflammopharmacology (2001), 9(1-2), 81-89
CODEN: IAOAES; ISSN: 0925-4692
PUBLISHER: VSP BV
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review, with refs. Nimesulide is a selective **COX-2 inhibitor** used in a variety of inflammatory, pain and fever states. After oral administration the drug is rapidly and extensively absorbed. Nimesulide is rapidly distributed, extensively bound to albumin and eliminated with a terminal half-life of about 4 h. Excretion of the unchanged drug in urine and feces is negligible. Nimesulide is mainly cleared from the body by metabolic transformation and the principal active metabolite is the 4'-hydroxyl deriv. (MI). After oral administration, nimesulide shows linear pharmacokinetics in the dose range from 25 to 100 mg. The usual therapeutic regimen is 100 mg p.o. twice daily. The pharmacokinetic profiles of nimesulide and M1 in children and elderly do not differ from those of healthy young subjects. The pharmacokinetics of nimesulide and M1 are not altered in moderate renal impairment. Pharmacokinetic interactions between nimesulide and other drugs given in combination were absent or of no clin. significance.
REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L89 ANSWER 14 OF 24 HCAPLUS COPYRIGHT 2004 ACS on STN
Full Text | Citing References
ACCESSION NUMBER: 2001:463610 HCAPLUS
DOCUMENT NUMBER: 136:209827
TITLE: COX-2 overview
AUTHOR(S): Sato, Nobuhiro
CORPORATE SOURCE: Department of Gastroenterology, Juntendo University, Japan
SOURCE: Igaku no Ayumi (2001), 197(2), 123-127
CODEN: IGAYAY; ISSN: 0039-2359
PUBLISHER: Ishiyaku Shuppan
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: Japanese
AB A review, discussing the **metab**. and pathophysiol. role of COX-2 and pharmacol. of **COX-2 inhibitors**.

L89 ANSWER 15 OF 24 HCAPLUS COPYRIGHT 2004 ACS on STN
Full Text | Citing References
ACCESSION NUMBER: 2001:427624 HCAPLUS
DOCUMENT NUMBER: 135:251305

TITLE: Nimesulide: Overview of properties and applications
AUTHOR(S): Rainsford, K. D.
CORPORATE SOURCE: Biomedical Research Centre, Division of Biomedical Sciences, Sheffield Hallam University, Sheffield, S1 1WB, UK
SOURCE: Drugs of Today (2001), 37(Suppl. B, Nimesulide), 3-7
CODEN: MDACAP; ISSN: 0025-7656
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 11 refs. Nimesulide, a selective cyclooxygenase 2 (**COX-2**) **inhibitor**, has antiinflammatory and analgesic properties. It has a twin arom. ring structure and a relatively high pKa of approx. 6.5. This along with the moderate lipophilicity of nimesulide may confer it low irritant potential, thus allowing for good uptake into the upper gastrointestinal circulation. Like other nonsteroidal antiinflammatory drugs (NSAIDs), nimesulide undergoes phase I **metab**. via the cytochrome P450 system. The phenolic metabolites undergo phase II **metab**. to produce phenolic-glucuronides. Nimesulide has been found to have a good safety record esp. in the gastrointestinal tract and is indicated for relief of a variety of conditions involving inflammation and pain, such as osteoarthritis, musculoskeletal conditions and dysmenorrhea.

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L89 ANSWER 16 OF 24 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:411308 HCAPLUS
DOCUMENT NUMBER: 136:272426
TITLE: Cyclooxygenase-2: a novel target for cancer chemotherapy?
AUTHOR(S): Dempke, Wolfram; Rie, Christoph; Grothey, Axel; Schmoll, Hans-Joachim
CORPORATE SOURCE: Department of Hematology and Oncology, Martin-Luther-University Halle-Wittenberg, Halle/Saale, 06120, Germany
SOURCE: Journal of Cancer Research and Clinical Oncology (2001), 127(7), 411-417
CODEN: JCROD7; ISSN: 0171-5216
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Epidemiol. studies have documented a 40-50% redn. in incidence of colorectal cancer in individuals taking nonsteroidal antiinflammatory drugs (NSAIDs). Since NSAIDs are known to inhibit cyclooxygenases (COX-1, COX-2), the basic mechanism of their antitumor effects is conceivably the altered **metab**. of arachidonic acid and, subsequently, prostaglandins (PGs). Although COX-2, the inducible isoform, is regularly expressed at low levels in colonic mucosa, its activity increases dramatically following mutation of the APC (adenomatous polyposis coli) gene suggesting that β-catenin/T-cell factor mediated Wnt-signaling activity may regulate COX-2 gene expression. In addn., hypoxic conditions and Na butyrate exposure may also contribute to COX-2 gene transcription in human cancers. The development of selective **COX-2 inhibitors** has made it possible to further evaluate the role of COX-2 activity in colorectal carcinogenesis. To date, at least 5 mechanisms by which COX-2 contributes to tumorigenesis and the malignant phenotype of tumor cells were identified, including: (1) inhibition of apoptosis; (2) increased angiogenesis; (3) increased invasiveness; (4) modulation of

inflammation/immuno-suppression; and (5) conversion of procarcinogens to carcinogens. A clear pos. correlation between COX-2 expression and inhibition of apoptosis was established, assocd. with increased PGE2 levels resulting in modulation of pro- and anti-apoptotic factors (e.g., bcl-2, MAKs/ras, caspase-3, Par-4). In terms of angiogenesis and invasiveness, COX-2 activity was found to increase the expression of growth factors (e.g., VDEG, PDGF, bFGF) and matrix metalloproteinases (MMPs). Since **COX-2 inhibitors** were demonstrated to interfere with tumorigenesis and apoptosis, COX-2 and its gene product may be attractive targets for therapeutic and chemoprotective strategies in colorectal cancer patients. This may lead to new perspectives that by controlling the cancer phenotype, rather than attempting to eradicate all affected cells, may provide significant benefits to the cancer patient.

REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L89 ANSWER 17 OF 24 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:400485 HCAPLUS
DOCUMENT NUMBER: 136:160669
TITLE: Recent progress in aspirin-induced asthma
AUTHOR(S): Sakakibara, Hiroki
CORPORATE SOURCE: Department of Allergy and Internal Medicine, Fujita Health and Hygiene University, Japan
SOURCE: Annual Review Kokyuki (2000) 82-92
CODEN: ARKNC8
PUBLISHER: Chugai Igakusha
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: Japanese

AB A review. Aspirin-induced asthma (AIA) is a distinct clin. syndrome in which bronchoconstrictive responses to nonsteroidal anti-inflammatory drugs (NSAIDs) can be predicted on the basis of their in vitro activity as inhibitors of cyclooxygenase, i.e. AIA is assocd. with alterations in arachidonate **metab**. In this review, several explanations are presented including peptidoleukotrienes overprodn., overexpression of leukotriene C4 (LTC4) synthase in bronchial cells, 5-lipoxygenase and LTC4 synthase gene promoter polymorphism, PGE2 dependency, role of the mast cells, and specific **COX-2 inhibitors**.

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Full Text | Citing References

ACCESSION NUMBER: 2001:160638 HCAPLUS
DOCUMENT NUMBER: 135:146593
TITLE: Cannabis and eicosanoids: A review of molecular pharmacology
AUTHOR(S): McPartland, John M.
CORPORATE SOURCE: Department of Family Practice, University of Vermont College of Medicine, Middlebury, VT, 05753, USA
SOURCE: Journal of Cannabis Therapeutics (2001), 1(1), 71-83
CODEN: JCTOAE; ISSN: 1529-9775
PUBLISHER: Haworth Press
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 40 refs. Many constituents of cannabis exhibit beneficial anti-inflammatory properties, such as Δ9-tetrahydrocannabinol (THC) in marijuana and gamma-linolenic acid (GLA) in hemp seed oil. The effects of these cannabis constituents on eicosanoid **metab**. is reviewed. THC and GLA modulate the arachidonic acid cascade, inhibiting the prodn. of

series 2 prostaglandins and series 4 leukotrienes. Cannabinoid receptor- as well as non-receptor-mediated signal transduction pathways appear to be involved. It is proposed that THC acts as a selective cyclooxygenase-2 (**COX-2**) **inhibitor**.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L89 ANSWER 19 OF 24 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:26538 HCAPLUS
DOCUMENT NUMBER: 134:231402
TITLE: The role of cyclooxygenase and lipoxygenase in cancer chemoprevention
AUTHOR(S): Cuendet, Muriel; Pezzuto, John M.
CORPORATE SOURCE: Program for Collaborative Research in Pharmaceutical Sciences and Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, IL, 60612, USA
SOURCE: Drug Metabolism and Drug Interactions (2000), 17(1-4), 109-157
CODEN: DMDIEQ; ISSN: 0792-5077
PUBLISHER: Freund Publishing House Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 274 refs. The involvement of prostaglandins (PGs) and other eicosanoids in the development of human cancer has been known for over two decades. Importantly, an increase in PG synthesis may influence tumor growth in human beings and exptl. animals, and numerous studies have illustrated the effect of PG synthesis on carcinogen **metab**., tumor cell proliferation and metastatic potential. PGs produced by cyclooxygenases (COXs) are represented by a large series of compds. that mainly enhance cancer development and progression, acting as carcinogens or tumor promoters, with profound effects on carcinogenesis. Further investigations suggest that arachidonic acid (AA) metabolites derived from lipoxygenase (LOX) pathways play an important role in growth-related signal transduction, implying that intervention through these pathways should be useful for arresting cancer progression. We discuss here the implications of COX and LOX in colon, pancreatic, breast, prostate, lung, skin, urinary bladder and liver cancers. Select inhibitors of COX and LOX are described, including nonsteroidal antiinflammatory drugs (NSAIDs), selective **COX-2 inhibitors**, curcumin, tea, silymarin and resveratrol, as well as a method useful for evaluating inhibitors of COX. Although a substantial amt. of addnl. work is required to yield a better understanding of the role of COX and LOX in cancer chemoprevention, it is clear that beneficial therapeutic effects can be realized through drug-mediated modulation of these metabolic pathways.

REFERENCE COUNT: 274 THERE ARE 274 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L89 ANSWER 20 OF 24 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2000:829704 HCAPLUS
DOCUMENT NUMBER: 134:172564
TITLE: A causal relationship between unscheduled eicosanoid signaling and tumor development: cancer chemoprevention by inhibitors of arachidonic acid **metabolism**

AUTHOR(S): Marks, F.; Muller-Decker, K.; Furstenberger, G.
CORPORATE SOURCE: German Cancer Research Center, Research Program Tumor Cell Regulation, Heidelberg, 69120, Germany
SOURCE: Toxicology (2000), 153(1-3), 11-26
CODEN: TXCYAC; ISSN: 0300-483X
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 97 refs. Cancer results from disturbances of cellular signal transduction and data processing at the genetic and epigenetic level. In the early phase of the disease these disturbances are mainly caused by environmental toxic agents, i.e. genotoxic and non-genotoxic carcinogens, whereas endogenous agents derived from dys-regulated metabolic reactions may take over this role at later stages, thereby leading to a state of 'genetic instability' and 'growth autonomy'. Among these metabolic reactions becoming dys-regulated in the course of tumorigenesis, eicosanoid biosynthesis from arachidonic acid seems to play a particular role. A steadily increasing body of evidence indicates a causal relationship between cancer development and an abnormal overexpression of eicosanoid-forming enzymes, i.e. cyclooxygenases and lipoxygenases, in a wide variety of human and animal tumors. This overexpression seems to result from disturbances of cellular signaling cascades such as the Ras-Raf-MAPkinase cascade due to oncogenic gene mutations. Presently, research is focussed on the pro-inflammatory enzyme cyclooxygenase-2 (COX-2) the pathol. overexpression of which has been found to be related to key events of tumor promotion such as cellular hyperproliferation, inhibition of programmed cell death, and tumor angiogenesis. In the mouse skin model of multistage carcinogenesis COX-2-derived prostaglandin F2α has been identified as an endogenous tumor promoter. Moreover, genotoxic byproducts of both cycloxygenase and lipoxygenase-catalyzed arachidonic acid **metab**. (such as active oxygen species, free radicals etc.) are suspected to contribute to 'genetic instability' and thus to malignant progression of tumor cells. The enzymes of eicosanoid biosynthesis rank therefore among the most attractive targets for cancer chemoprevention. In fact, both nonsteroidal antiinflammatory drugs, i.e. non-specific COX inhibitors, and isoenzyme-specific **COX-2 inhibitors** have been shown to inhibit exptl. and human cancer development, in the latter case in particular in the large bowel. Beside their role as indicators of neoplastic development eicosanoids may be also used as reporters of skin irritation. Based to this concept an in vitro test system for skin toxicity has been developed in which the release of arachidonic acid and interleukin-1α, i.e. two key mediators of acute inflammation, from a human keratinocyte cell line is measured. The excellent correlation found between this mediator release and the effects of various chem. irritants on human skin in vivo indicates that, in the near future, this and related methods may help to do without animal expts. in toxicol. testing.

REFERENCE COUNT: 97 THERE ARE 97 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L89 ANSWER 21 OF 24 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2000:753914 HCAPLUS
DOCUMENT NUMBER: 134:275214
TITLE: Defining **COX-2 inhibitors**
AUTHOR(S): Lipsky, Peter E.
CORPORATE SOURCE: University of Texas Southwestern Medical Center at Dallas, Dallas, TX, 75235-8884, USA
SOURCE: Journal of Rheumatology, Supplement (2000),

60(Advances in Arthritis Care: From Current Therapeutic Options to Specific COX-2 Inhibition), 13-16
CODEN: JRSUDX; ISSN: 0380-0903
PUBLISHER: Journal of Rheumatology Publishing Co. Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 16 refs. Arachidonic acid **metab**. is governed by 2 isoforms of cyclooxygenase (COX): the constitutively expressed COX-1 and the inducible COX-2. The anti-inflammatory, analgesic, and antipyretic effects of nonsteroidal anti-inflammatory drugs (NSAIDs) are explained by the capacity of these agents to inhibit COX-2, whereas the serious gastrointestinal side effects are caused by inhibitors of COX-1. The first of a new class of COX inhibitors, the COX-2-specific inhibitors, has just been approved for the treatment of osteoarthritis (OA) and rheumatoid arthritis (RA). As the clin. effects of specific **COX-2 inhibitors** are considerably different than those of NSAIDs, it is essential for the clinician to understand the basis of classification of those new, effective, and safer therapeutic agents for the treatment of OA and RA.

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L89 ANSWER 22 OF 24 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1999:249760 HCAPLUS
DOCUMENT NUMBER: 131:100522
TITLE: Metabolic targets of cancer chemoprevention: Interruption of tumor development by inhibitors of arachidonic acid **metabolism**
AUTHOR(S): Marks, F.; Furstenberger, G.; Muller-Decker, K.
CORPORATE SOURCE: Tumor Cell Regulation, Department B 0500, German Cancer Research Center, Heidelberg, D-69120, Germany
SOURCE: Recent Results in Cancer Research (1999), 151(Chemoprevention of Cancer), 45-67
CODEN: RRCRBU; ISSN: 0080-0015
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with over 100 refs. Tumor promotion is understood as a process that favors the clonal outgrowth of single mutated (initiated) cells to premalignant lesions through co-mitogenic and anti-apoptotic effects. This process can be evoked by repeated induction of a regenerative tissue response as achieved either by irritation and wounding or by agents (tumor promoters) that interact with the corresponding pathways of cellular signaling. Metabolic processes regulated by such pathways and essential for tumor development are potential targets of cancer chemoprevention. Examples are provided by the expression of ornithine decarboxylase and the activation of eicosanoid formation from arachidonic acid. Arachidonic acid **metab**. is a particularly attractive and important target of chemopreventive measures. Its induction is a characteristic response to tissue damage and irritation and an apparently crit. event in epithelial tumor promotion. Inhibitors of eicosanoid formation, such as nonsteroidal anti-inflammatory drugs, rank among the most powerful chemopreventive agents in animal models and have been shown to halve the incidence of colorectal cancer in man. Recently, the role of cyclooxygenase-2 (COX-2)-catalyzed prostaglandin synthesis has been the subject of much attention. COX-2 is a typical 'emergency enzyme', since in most tissues it is transiently induced only in the course of repair and defense reactions. In epithelial neoplasia, i.e. in skin and colorectal tumors,

the enzyme is constitutively overexpressed along different mol. pathways, and it seems to be critically involved in tumor promotion. Consequently, specific **COX-2 inhibitors** have been shown to exhibit considerable cancer chemopreventive potential. The putative role of other pathways of arachidonic acid **metab**. in tumor promotion and malignant progression is presently under investigation.

REFERENCE COUNT: 109 THERE ARE 109 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L89 ANSWER 23 OF 24 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1998:744356 HCAPLUS
DOCUMENT NUMBER: 130:148047
TITLE: Cyclooxygenase-2 inhibitors in tumorigenesis (part II)
AUTHOR(S): Taketo, Makoto M.
CORPORATE SOURCE: Laboratory of Biomedical Genetics, Graduate School of PharmaceuticalSciences, University of Tokyo, Tokyo, 113-0033, Japan
SOURCE: Journal of the National Cancer Institute (1998), 90(21), 1609-1620
CODEN: JNCIEQ; ISSN: 0027-8874
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 146 refs. The rate-limiting step in arachidonate **metab**. is mediated by enzymes known as cyclooxygenases (COXs). These enzymes catalyze the biosynthesis of prostaglandin H2, the precursor of mols. such as prostaglandins, prostacyclin, and thromboxanes. The COX enzyme family consists of the classical COX-1 enzyme, which is constitutively expressed in many tissues, and a second isoenzyme, i.e., COX-2, which is induced by various stimuli, such as mitogens and cytokines, and is involved in many inflammatory reactions. Because nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit both COX-1 and COX-2, these drugs also cause unwanted side effects, exemplified by gastrointestinal bleeding. Accumulating evidence indicates that NSAIDs can reduce the incidence of colorectal cancers in human and exptl. animals and can reduce the no. and size of polyps in patients with familial adenomatous polyposis. This Part II (of a two-part review) focuses on the growing clin. and exptl. evidence that NSAIDS and **COX-2 inhibitors** can influence the risk of colon (and possibly of other) cancers.

REFERENCE COUNT: 149 THERE ARE 149 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L89 ANSWER 24 OF 24 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1995:484437 HCAPLUS
DOCUMENT NUMBER: 122:229967
TITLE: Arachidonic acid **metabolism** and inflammation. Anti-inflammatory drugs with selective inhibition of cyclooxygenase (COX)-2
AUTHOR(S): Otomo, Susumu; Higuchi, Shohei; Futaki, Nobuko
CORPORATE SOURCE: Res. Cent., Taisyo Pharm. Co., Ltd., Omiya, 330, Japan
SOURCE: Ensho to Men'eki (1994), 3(1), 29-36
CODEN: ENMEFA; ISSN: 0918-8371
PUBLISHER: Sentan Igakusha
DOCUMENT TYPE: Journal; **General Review**

LANGUAGE: Japanese
AB A review with 30 refs. on **COX-2 inhibition** by nonsteroidal antiinflammatory drugs (NSAIDs).

=> s l1 and toxin?
106807 TOXIN?
L90 36 L1 AND TOXIN?

=> s l90 and review/dt
1734424 REVIEW/DT
L91 2 L90 AND REVIEW/DT

=> d l91, ibib abs, 1-2

L91 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN
Full Text | Citing References
ACCESSION NUMBER: 2002:804187 HCAPLUS
DOCUMENT NUMBER: 138:202384
TITLE: Oxidative stress in brain aging Implications for therapeutics of neurodegenerative diseases
AUTHOR(S): Floyd, Robert A.; Hensley, Kenneth
CORPORATE SOURCE: Free Radical Biology and Aging Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, 73104, USA
SOURCE: Neurobiology of Aging (2002), 23(5), 795-807
CODEN: NEAGDO; ISSN: 0197-4580
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. Age has a powerful effect on enhanced susceptibility to neurodegenerative diseases, including susceptibility to stroke and cognitive impairment (CI) even in optimally healthy individuals. We critically evaluated the notion that oxidative stress increases in aging brain. Rigorous studies show logarithmic age-dependent increases in oxidized proteins and oxidized DNA lesions. Decreased activity of antioxidant protective enzymes does not account for the obsd. increases. The reactivity of the lipid oxidn. product 4-hydroxy-2-nonenal (HNE) with key mitochondria enzymes may be important in the age-dependent loss in energy generation and enhanced susceptibility of neurons to apoptosis. Age-dependent enhanced neuroinflammatory processes may play an important role in **toxin** generation that causes death or dysfunction of neurons in neurodegenerative diseases. Non-steroidal anti-inflammatory drugs (NSAIDs) show significant promise. Vitamin E supplementation did not show major beneficial effect on cognitive functions. Major clin. trials for Alzheimer's disease (AD) involving cycloxygenase-II (COX II) inhibitors and amyloid-beta vaccination have been discontinued. Novel therapeutics based on blocking neuron damaging neuroinflammatory processes show great promise for abating dementia progression although they have yet to make it to clin. practice.
REFERENCE COUNT: 121 THERE ARE 121 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN
Full Text | Citing References
ACCESSION NUMBER: 2000:75849 HCAPLUS
DOCUMENT NUMBER: 133:37

TITLE: Do cyclooxygenase-2 inhibitors provide benefits similar to those of traditional nonsteroidal anti-inflammatory drugs, with less gastrointestinal toxicity?
AUTHOR(S): Feldman, Mark; McMahon, Alexander T.
CORPORATE SOURCE: Dallas Veterans Affairs Medical Center, Dallas, TX, 75216, USA
SOURCE: Annals of Internal Medicine (2000), 132(2), 134-143
CODEN: AIMEAS; ISSN: 0003-4819
PUBLISHER: American College of Physicians-American Society of Internal Medicine
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review and discussion with 73 refs. Two forms of cyclooxygenase, cyclooxygenase-1 (COX-1) and cyclooxygenase 2 (COX-2), act as rate-limiting enzymes in prostaglandin and thromboxane synthesis. Discovery of these compds. led to the development of drugs that selectively or specifically inhibit the COX-2 isoform. Although the COX-1 isoform is expressed at fairly const. levels in cells, including the gastrointestinal mucosa and platelets, expression of COX-2 varies greatly. In many cells, low expression of COX-2 can be upregulated by various stimuli, including inflammatory cytokines, bacterial **toxins**, and growth factors; this suggests that COX-2 plays a role in inflammation, infection, and cellular proliferation. It was thought that newly developed drugs designed to block COX-2 but not COX-1 would have anti-inflammatory properties and would avoid inhibiting the synthesis of gastrointestinal prostaglandins (thereby avoiding ulcers) and platelet thromboxane (thereby avoiding bleeding). Gastrointestinal ulcers and bleeding are side effects of traditional nonsteroidal anti-inflammatory drugs (NSAIDs) that block COX-1 and COX-2. Meloxicam and nimesulide, selective **COX-2 inhibitors** available outside the United States, are as effective as traditional NSAIDs but have similar gastrointestinal side effects. Celecoxib (Celebrex, G.D. Searle and Co., Chicago, Illinois) and rofecoxib (Vioxx, Merck and Co., Inc., West Point, Pennsylvania), selective **COX-2 inhibitors** approved in the United States in the past year, are also as effective as traditional NSAIDs. However, celecoxib and rofecoxib have no antiplatelet activity and lead to fewer endoscopically detected gastric and duodenal ulcers than traditional NSAIDs, such as ibuprofen or naproxen. Preliminary analyses of data pooled from several trials suggest that celecoxib and rofecoxib are assocd. with fewer clin. symptomatic ulcers and ulcer complications than traditional NSAIDs are. Postmarketing surveillance should help clarify the actual risk for serious ulcer complications with these new **COX-2 inhibitors** and reveal other potential nongastrointestinal toxic reactions that can result from their use.

REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> s l1 and anoxi?
         17007 ANOXI?
L92          4 L1 AND ANOXI?

=> s l92 and review/dt
       1734424 REVIEW/DT
L93          0 L92 AND REVIEW/DT

=> s l1 and vitamin? () defic?
        192572 VITAMIN?
        317409 DEFIC?
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          2073 VITAMIN? (W) DEFIC?
L94          0 L1 AND VITAMIN? (W) DEFIC?

=> s l1 and vitamin?
        192572 VITAMIN?
L95         28 L1 AND VITAMIN?

=> s l95 and review/dt
       1734424 REVIEW/DT
L96          3 L95 AND REVIEW/DT

=> d l96, ibib abs, 1-3

L96  ANSWER 1 OF 3  HCAPLUS  COPYRIGHT 2004 ACS on STN
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Full Text | Citing References

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ACCESSION NUMBER:         2002:804187  HCAPLUS
DOCUMENT NUMBER:          138:202384
TITLE:                    Oxidative stress in brain aging Implications for
                          therapeutics of neurodegenerative diseases
AUTHOR(S):                Floyd, Robert A.; Hensley, Kenneth
CORPORATE SOURCE:         Free Radical Biology and Aging Research Program,
                          Oklahoma Medical Research Foundation, Oklahoma City,
                          OK, 73104, USA
SOURCE:                   Neurobiology of Aging (2002), 23(5), 795-807
                          CODEN: NEAGDO; ISSN: 0197-4580
PUBLISHER:                Elsevier Science Inc.
DOCUMENT TYPE:            Journal; General Review
LANGUAGE:                 English
AB   A review.  Age has a powerful effect on enhanced susceptibility to
     neurodegenerative diseases, including susceptibility to stroke and
     cognitive impairment (CI) even in optimally healthy individuals.  We
     critically evaluated the notion that oxidative stress increases in aging
     brain.  Rigorous studies show logarithmic age-dependent increases in
     oxidized proteins and oxidized DNA lesions.  Decreased activity of
     antioxidant protective enzymes does not account for the obsd. increases.
     The reactivity of the lipid oxidn. product 4-hydroxy-2-nonenal (HNE) with
     key mitochondria enzymes may be important in the age-dependent loss in
     energy generation and enhanced susceptibility of neurons to apoptosis.
     Age-dependent enhanced neuroinflammatory processes may play an important
     role in toxin generation that causes death or dysfunction of neurons in
     neurodegenerative diseases.  Non-steroidal anti-inflammatory drugs
     (NSAIDs) show significant promise.  Vitamin E supplementation did not
     show major beneficial effect on cognitive functions.  Major clin. trials
     for Alzheimer's disease (AD) involving cycloxygenase-II (COX II)
     inhibitors and amyloid-beta vaccination have been discontinued.  Novel
     therapeutics based on blocking neuron damaging neuroinflammatory processes
     show great promise for abating dementia progression although they have yet
     to make it to clin. practice.
REFERENCE COUNT:          121   THERE ARE 121 CITED REFERENCES AVAILABLE FOR
                                THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
                                FORMAT

L96  ANSWER 2 OF 3  HCAPLUS  COPYRIGHT 2004 ACS on STN
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Full Text | Citing References

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ACCESSION NUMBER:         2002:162784  HCAPLUS
DOCUMENT NUMBER:          137:194801
TITLE:                    Cancer chemoprevention - present and future
AUTHOR(S):                Fujiki, Hirota; Suganuma, Masami
```

CORPORATE SOURCE: Saitama Cancer Center, Japan
SOURCE: Biotherapy (Tokyo, Japan) (2002), 16(1), 1-9
CODEN: BITPE9; ISSN: 0914-2223
PUBLISHER: Gan to Kagaku Ryohosha
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: Japanese

AB A review with refs. The term "cancer chemoprevention", defined as prevention of the occurrence of cancer by administration of one or more compds., was coined by Michael B. Sporn in 1976. The significance of cancer chemoprevention is now internationally accepted, and interest in Japan is accelerating. This article looks at notable results of clin. trials conducted in the U.S. and Europe, and touches upon research activities in Japan. The good news includes promising results on cancer prevention in the breast, colon and liver. Main topics: 1) Breast cancer prevention trials with tamoxifen have provided effective results for individuals in the high risk group, patients with premalignant lesions-ductal carcinoma in situ (DCIS) - and contralateral breast cancer patients. 2) Primary lung cancer prevention trials with alpha-tocopherol, β-carotene (ATBC) in Finland, and with β-carotene and retinol (CARET) in the U.S., showed an unexpected increase in lung cancer incidence, and recently reported results of a EUROSCAN study did not show any benefits from **vitamin** A and N-acetylcysteine. These three major studies indicate that a new approach is required. 3) Encouraging results with prostate cancer prevention by finasteride are anticipated. 4) The FDA has approved celecoxib, a selective **Cox-2 inhibitor**, for the prevention of polyp development in patients with familial adenomatous polyposis. 5) Acyclic retinoid, polyprenoic acid prevented second primary hepatomas after surgical resection of the original tumor or percutaneous injection of ethanol, mediated through clonal deletion of malignant cells in the remnant liver. 6) Finally, we discuss cancer prevention with green tea. Based on results of basic studies of (-)-epigallocatechin gallate (EGCG) and green tea polyphenols, and also results of a prospective cohort study with 8,552 individuals, we are now moving toward prevention of cancer in various organs (both primary tumor and recurrence) by introducing the "Saitama System": the equiv. of 10 Japanese-size cups of green tea per day (2.5 g green tea ext. per day) in a combination of daily beverage and green tea tablets. It is our hope that this article will provide information that will spur an increase in cancer prevention trials in Japan.

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Full Text | Citing References

ACCESSION NUMBER: 2001:408183 HCAPLUS
DOCUMENT NUMBER: 135:55329
TITLE: Pharmacology of fetal ductus arteriosus
AUTHOR(S): Momma, Kazuo
CORPORATE SOURCE: Dep. Pediatr. Cardiol., Sch. Med., Tokyo Women's Med. Univ., Japan
SOURCE: Tokyo Joshi Ika Daigaku Zasshi (2001), 71(4), 263-269
CODEN: TJIZAF; ISSN: 0040-9022
PUBLISHER: Tokyo Joshi Ika Daigaku Gakkai
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: Japanese

AB A review with 25 refs. Fetal ductus arteriosus is widely patent, permitting 90% of right ventricular output flowing to the descending aorta in the fetus. Until 1990, only low pO2 and prostaglandins were known as factors which maintain dilatation of fetal ductus arteriosus. Only recently, other factors which control fetal ductal tone have been discovered. Nitric oxide is the important factor which maintains patency

of the fetal ductus. The major role of nitric oxide is to maintain ductal patency in mid-gestation, when prostaglandins is not working. In late gestation, the role of nitric oxide in maintaining fetal ductal patency switches to prostaglandins. Prostaglandins are produced by cyclooxygenase (COX) 1 and 2. COX-2 is important in maintaining ductal patency, and therapeutic use of selective **COX-2 inhibitors** in closing patent ductus arteriosus in premature baby is recommended. **Vitamin** A increases sensitivity of ductal sensitivity to oxygen and ductal constriction by indomethacin. Endothelin is essential in fetal ductal constriction, and pharmacol. fetal ductal constriction is completely prevented by endothelin blockers such as Bosentan.

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=> s l1 and mild () cogn? () impair?
         98018 MILD
             4 MILDS
         98020 MILD
                 (MILD OR MILDS)
         25680 COGN?
        121099 IMPAIR?
           186 MILD (W) COGN? (W) IMPAIR?
L97          4 L1 AND MILD (W) COGN? (W) IMPAIR?

=> s l97 and review/dt
       1734424 REVIEW/DT
L98          2 L97 AND REVIEW/DT

=> d l98, ibib abs, 1-2

L98  ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2004 ACS on STN
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Full Text | Citing References

ACCESSION NUMBER: 2002:795379 HCAPLUS
DOCUMENT NUMBER: 138:313675
TITLE: From cyclooxygenase activities to Alzheimer's disease neuropathology: experimental approaches and therapeutic interventions
AUTHOR(S): Pasinetti, Giulio Maria
CORPORATE SOURCE: Neuroinflammation Research Laboratories, Department of Psychiatry, Mount Sinai School of Medicine, New York, NY, 10029, USA
SOURCE: Drug Development Research (2002), 56(3), 438-445
CODEN: DDREDK; ISSN: 0272-4391
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Several prospective and retrospective epidemiol. studies have demonstrated a protective effect for antiinflammatory drugs in Alzheimer's disease (AD). However, despite this evidence therapeutic studies investigating nonsteroidal antiinflammatory drugs (NSAIDs), including cyclooxygenase (COX)-1 and **COX-2 inhibitors** and steroids, do not support this hypothesis. This discrepancy may be due to the fact that the bulk of epidemiol. evidence has examd. the likely incidence of AD prior to the onset of clin. symptoms of disease. In contrast, in therapeutic studies NSAIDs are administered to patients with illnesses severe enough to exceed the clin. detection threshold, suggesting that NSAID therapy administered following the onset of AD may not be optimally effective. Thus, patients at high risk for AD, e.g., those with **mild cognitive impairment** (MCI), may be more suitable for study in clin. trials of NSAIDs. Indeed, recent evidence suggests that different indexes of

classical inflammatory cascades have distinct assocns. with different phases of the clin. progression of AD. In this review, I discuss the potential role of inflammation in the clin. progression of AD and how this evidence relates to preventive use of antiinflammatory drugs for AD treatment. I then examine the importance of evidence for the potential role of inflammation in amyloidosis in the AD brain and exptl. models. I consider the implications of inflammation in AD and recent evidence potentially supporting a neg. role of inflammation in vaccination therapy trials. In conclusion, I examine cutting-edge clin. studies investigating NSAID therapy for AD.

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L98 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:266015 HCAPLUS
DOCUMENT NUMBER: 135:40287
TITLE: The status of ongoing trials for **mild cognitive impairment**
AUTHOR(S): Sramek, John J.; Veroff, Amy E.; Cutler, Neal R.
CORPORATE SOURCE: California Clinical Trials, Beverly Hills, CA, USA
SOURCE: Expert Opinion on Investigational Drugs (2001), 10(4), 741-752
CODEN: EOIDER; ISSN: 1354-3784
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 82 refs. **Mild cognitive impairment** (MCI) is a term used to describe memory decline or other specific cognitive impairment in individuals who do not have dementia or significant impairment of other cognitive functions beyond that expected for their age or education. It has been suggested that as much as 38% of the elderly population would meet criteria for MCI and although the assocd. memory deficits are mild, the fact that up to 15% of MCI patients, particularly those with a particular type of memory impairment, convert to Alzheimer's disease (AD) annually has prompted serious attention. Despite the high conversion rate, MCI cannot be used synonymously with early or mild AD, as patients with AD are impaired not only in memory performance but in other cognitive domains as well; they meet diagnostic criteria for dementia. However, since there is a high conversion rate from MCI to AD, it is likely many with MCI have the underlying neuropathol. of AD, though they do not yet meet clin. diagnostic criteria. Therefore, treatment strategies developed for AD, specifically acetylcholinesterase inhibitors and **Cox-2 inhibitors**, have been among the first employed to treat MCI. It is hoped that by impeding the progression of MCI in this manner, fewer patients will convert to AD. This article will give a brief overview of the condition of **mild cognitive impairment** and an account of trial methodol. and current treatment strategies being employed for MCI.

REFERENCE COUNT: 82 THERE ARE 82 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> s l1 and alzheim? () disease?
         30349 ALZHEIM?
        781585 DISEASE?
         11901 ALZHEIM? (W) DISEASE?
L99         25 L1 AND ALZHEIM? (W) DISEASE?

=> s l99 and review/dt
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       1734424 REVIEW/DT
L100         12 L99 AND REVIEW/DT

=> d l100, ibib abs fhitstr, 1-12

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Full Text | Citing References

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ACCESSION NUMBER:         2003:969627  HCAPLUS
DOCUMENT NUMBER:          140:399058
TITLE:                    Experimental brain inflammation and neurodegeneration
                          as model of alzheimer's disease: protective effects of
                          selective COX-2 inhibitors
AUTHOR(S):                Giovannini, M. G.; Scali, C.; Prosperi, C.; Bellucci,
                          A.; Pepeu, G.; Casamenti, F.
CORPORATE SOURCE:         Dipartimento di Farmacologia Preclinica e Clinica
                          "Mario Aiazzi Mancini", Universita di Firenze,
                          Florence, 50139, Italy
SOURCE:                   International Journal of Immunopathology and
                          Pharmacology (2003), 16(2, Suppl.), 31-40
                          CODEN: IJIPE4; ISSN: 0394-6320
PUBLISHER:                Biolife s.a.s.
DOCUMENT TYPE:            Journal; General Review
LANGUAGE:                 English
AB   A review.  Epidemiol. studies indicate that long-term treatment with non
     steroidal anti-inflammatory drugs reduces the risk of Alzheimer
     Disease and may delay its onset or slow its progression.
     Neuroinflammation occurs in vulnerable regions of the Alzheimer's disease
     (AD) brain where highly insol. β-amyloid (Aβ) peptide deposits
     and neurofibrillary tangles, as well as damaged neurons and neurites,
     provide stimuli for inflammation.  To elucidate the complex role of
     inflammation in neurodegenerative processes and the efficacy of selective
     COX-2 inhibitors in AD we examd. whether the attenuation of brain
     inflammatory reaction by selective COX-2 inhibitors may protect
     neurons against neurodegeneration.  The data reported in this review show
     that in in vivo models of brain inflammation and neurodegeneration, the
     administration of selective COX-2 inhibitors prevent not only the
     inflammatory reaction, but also the cholinergic hypofunction.  Our data
     may help elucidating the epidemiol. findings indicating that
     anti-inflammatory agents, in particular NSAIDs, reduce the risk of
     developing AD and may slow its progression.
REFERENCE COUNT:          44    THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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Full Text | Citing References

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ACCESSION NUMBER:         2003:540010  HCAPLUS
DOCUMENT NUMBER:          139:345166
TITLE:                    Non-steroidal anti-inflammatory drugs and
                          cyclooxygenase in Alzheimer's disease
AUTHOR(S):                Hoozemans, Jeroen J. M.; Veerhuis, Robert; Rozemuller,
                          Annemieke J. M.; Eikelenboom, Piet
CORPORATE SOURCE:         Department of Pathology, Graduate School Neurosciences
                          Amsterdam, Research Institute Neurosciences, VU
                          University Medical Center, Amsterdam, Neth.
SOURCE:                   Current Drug Targets (2003), 4(6), 461-468
                          CODEN: CDTUAU; ISSN: 1389-4501
PUBLISHER:                Bentham Science Publishers Ltd.
DOCUMENT TYPE:            Journal; General Review
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LANGUAGE: English

AB A review. Epidemiol. studies indicate that anti-inflammatory drugs, esp. the non-steroidal anti-inflammatory drugs (NSAIDs), decrease the risk of developing Alzheimer's disease (AD). Their beneficial effects may be due to interference in the chronic inflammatory reaction, that takes place in AD. The best-characterized action of NSAIDs is the inhibition of cyclooxygenase (COX). There is special interest for anti-inflammatory treatment of AD using selective **COX-2 inhibitors**. These inhibitors reduce the inflammatory reaction but lack the side effects obsd. with non-selective NSAIDs. So far, clin. trials designed to inhibit inflammation or COX-2 activity have failed in the treatment of AD patients. Several lines of evidence can explain the failures of the anti-inflammatory and anti-COX-2 trials on AD patients. In this review we will focus on the role, expression and regulation of COX-1 and COX-2 in AD brain. Understanding the role of COX in AD pathogenesis could contribute to the development of an anti-inflammatory therapy for the treatment or prevention of AD.

REFERENCE COUNT: 79 THERE ARE 79 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L100 ANSWER 3 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:33554 HCAPLUS
DOCUMENT NUMBER: 139:46145
TITLE: Cyclooxygenase as a Target for the Antiamyloidogenic Activities of Nonsteroidal Anti-Inflammatory Drugs in Alzheimer's Disease
AUTHOR(S): Pasinetti, Giulio Maria
CORPORATE SOURCE: Department of Psychiatry, Neuroinflammation Research Laboratories, Mount Sinai Medical Center, New York, NY, USA
SOURCE: Neurosignals (2002), 11(5), 293-297
CODEN: NEURIQ; ISSN: 1424-862X
PUBLISHER: S. Karger AG
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. A large no. of epidemiol. studies have addressed the possible protective effect of anti-inflammatory drug use with regard to Alzheimer's disease (AD). The most convincing of these studies - the Baltimore Longitudinal Study of Aging - utilized data collected prospectively, thereby minimizing recall bias issues. However, despite this evidence, therapeutic studies investigating nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase-1 (COX-1) and **COX-2 inhibitors** and steroids, do not support this hypothesis. This discrepancy may be due to the fact that the bulk of epidemiol. evidence has examd. the likely incidence of AD prior to the onset of clin. symptoms of disease. On the basis of this information, the article will attempt to formulate a possible scenario, in which optimal NSAIDs might be tested in the most favorable clin. therapeutic conditions in order to det. whether NSAIDs can provide beneficial treatment for the clin. progression of AD dementia.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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ACCESSION NUMBER: 2002:795379 HCAPLUS
DOCUMENT NUMBER: 138:313675
TITLE: From cyclooxygenase activities to Alzheimer's disease

neuropathology: experimental approaches and therapeutic interventions
AUTHOR(S): Pasinetti, Giulio Maria
CORPORATE SOURCE: Neuroinflammation Research Laboratories, Department of Psychiatry, Mount Sinai School of Medicine, New York, NY, 10029, USA
SOURCE: Drug Development Research (2002), 56(3), 438-445
CODEN: DDREDK; ISSN: 0272-4391
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review. Several prospective and retrospective epidemiol. studies have demonstrated a protective effect for antiinflammatory drugs in Alzheimer's disease (AD). However, despite this evidence therapeutic studies investigating nonsteroidal antiinflammatory drugs (NSAIDs), including cyclooxygenase (COX)-1 and **COX-2 inhibitors** and steroids, do not support this hypothesis. This discrepancy may be due to the fact that the bulk of epidemiol. evidence has examd. the likely incidence of AD prior to the onset of clin. symptoms of disease. In contrast, in therapeutic studies NSAIDs are administered to patients with illnesses severe enough to exceed the clin. detection threshold, suggesting that NSAID therapy administered following the onset of AD may not be optimally effective. Thus, patients at high risk for AD, e.g., those with mild cognitive impairment (MCI), may be more suitable for study in clin. trials of NSAIDs. Indeed, recent evidence suggests that different indexes of classical inflammatory cascades have distinct assocns. with different phases of the clin. progression of AD. In this review, I discuss the potential role of inflammation in the clin. progression of AD and how this evidence relates to preventive use of antiinflammatory drugs for AD treatment. I then examine the importance of evidence for the potential role of inflammation in amyloidosis in the AD brain and exptl. models. I consider the implications of inflammation in AD and recent evidence potentially supporting a neg. role of inflammation in vaccination therapy trials. In conclusion, I examine cutting-edge clin. studies investigating NSAID therapy for AD.
REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L100 ANSWER 5 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
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ACCESSION NUMBER: 2002:644548 HCAPLUS
DOCUMENT NUMBER: 138:147051
TITLE: Cycloxygenase-2 inhibitor nonsteroidal anti-inflammatory drugs: Current issues
AUTHOR(S): Kummer, Carmen Luize; Coelho, Tereza Cristina R. B.
CORPORATE SOURCE: Fisiologia Farmacologia, UFPE, Recife, 51020-390, Brazil
SOURCE: Revista Brasileira de Anestesiologia (2002), 52(4), 498-512
CODEN: RBANAV; ISSN: 0034-7094
PUBLISHER: Sociedade Brasileira de Anestesiologia
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: Portuguese/English
AB A review. Due to the high incidence of nonsteroidal anti-inflammatory drug (NSAID)-related side-effects, the discovery of 2 cycloxygenase isoforms (COX-1 constitutive and COX-2 inductive) has provided a new paradigm that the NSAID anti-inflammatory properties could be mediated by **COX-2 inhibition** and the side-effects by COX-1 blockade. The COX-2 is constitutively present in normal tissues, thus raising the question of

how really safe are specific inhibitors of this enzyme. New clin. and exptl. data on COX-2 and its specific inhibitors are discussed. New concepts of structural differences between COX-1 and COX-2, existence of these 2 isoforms in different animal and human body tissues, and clin. observations of specific **COX-2 inhibitors** are outlined. Potential new therapeutic indications of for NSAID in **Alzheimer disease** and cancer are emphasized. These drugs represent an important pharmacol. advance in anti-inflammatory treatment, decreasing the incidence of gastrointestinal adverse side-effects and probably playing a role in the prevention of cancer and neurol. diseases. Some side-effects similar to those of conventional NSAID still exist. The specific inhibitors are also rather high-cost drugs. Like any new medication, further studies are needed to det. the real safety profile of these compds.

REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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ACCESSION NUMBER: 2002:411415 HCAPLUS
DOCUMENT NUMBER: 137:179252
TITLE: Evaluation of selective **COX-2 inhibitors** for the treatment of Alzheimer's disease
AUTHOR(S): Aisen, Paul S.
CORPORATE SOURCE: Departments of Neurology and Medicine, Georgetown University Medical Center, Washington, DC, 20007, USA
SOURCE: Journal of Pain and Symptom Management (2002), 23(4S), S35-S40
CODEN: JPSMEU; ISSN: 0885-3924
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Alzheimer's disease (AD) is a worldwide problem that affects 5 million people in the United States alone. Until the approval of tacrine in the mid-1990s, there was no effective therapy for the cognitive symptoms of AD. Although cholinergic therapy provides modest but significant symptomatic relief, the development of effective disease-modifying therapy is essential. It has been demonstrated that a no. of inflammatory processes are active in the brain of patients with AD, and therefore it is believed that an anti-inflammatory regimen may offer some degree of neuroprotection. Several studies have indicated that use of nonsteroidal anti-inflammatory drugs (NSAIDs) is assocd. with delayed onset and/or slowed cognitive decline in AD. Although not currently approved for this condition, recent findings have demonstrated that cyclooxygenase (COX)-2 is of primary importance in the inflammatory response and may have a role in neurodegeneration. Therefore, selective **COX-2 inhibitors** (coxibs) may have an advantage over traditional NSAIDs as potential therapeutic agents in AD. The Alzheimer's Disease Cooperative Study (ADCS) is conducting an ongoing multicenter, double-blind, placebo-controlled trial to det. whether rofecoxib, a coxib, or naproxen, a nonselective NSAID, will slow the rate of cognitive and clin. decline in AD. This study, along with other clin. studies currently under way, will det. the utility of selective and nonselective COX inhibitors for the prevention and treatment of AD.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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ACCESSION NUMBER: 2000:616069 HCAPLUS
DOCUMENT NUMBER: 134:125382
TITLE: Progress with selective **COX-2 inhibitors**
AUTHOR(S): Jimenez, Juan-Miguel; Crespo, Maria Isabel; Godessart, Nuria
CORPORATE SOURCE: Centro de Investigacion, Almirall Prodesfarma, Barcelona, 08024, Spain
SOURCE: IDrugs (2000), 3(8), 907-919
CODEN: IDRUFN; ISSN: 1369-7056
PUBLISHER: Current Drugs Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 159 refs. on the selective inhibition of COX-2 by diaryl heterocycles, acidic sulfonamides, modified nonsteroidal antiinflammatory agents, and new therapeutic application of **COX-2 inhibitors** in cancer and **Alzheimer diseases**.
REFERENCE COUNT: 127 THERE ARE 127 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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Full Text | Citing References

ACCESSION NUMBER: 2000:588096 HCAPLUS
DOCUMENT NUMBER: 134:36565
TITLE: Cyclo-oxygenase-2 inhibitors: rationale and therapeutic potential for Alzheimer's disease
AUTHOR(S): McGeer, Patrick L.
CORPORATE SOURCE: Kinsmen Laboratory of Neurological Research, Department of Psychiatry, University of British Columbia, Vancouver, BC, Can.
SOURCE: Drugs & Aging (2000), 17(1), 1-11
CODEN: DRAGE6; ISSN: 1170-229X
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 52 refs. The newly introduced cyclo-oxygenase-2 (**COX-2**) **inhibiting** nonsteroidal anti-inflammatory drugs (NSAIDs) have been established as effective agents in treating arthritic conditions, while greatly reducing the gastrointestinal adverse effects of traditional NSAIDs. There are expectations that NSAIDs will be useful in the treatment of Alzheimer's disease (AD), and that **COX-2 inhibitors** might have a role. However, a recently reported clin. trial of a **COX-2 inhibitor** in AD indicated that it was neither protective nor did it accelerate the decline. The expectations were based on pathol. evidence of inflammatory changes assocd. with AD lesions and epidemiol. evidence of a reduced prevalence of AD in populations taking NSAIDs. They were supported by preliminary evidence showing efficacy of NSAIDs in treating patients with AD. These data are based on the use of traditional NSAIDs. Whether **COX-2 inhibitors** would be similarly effective was uncertain since COX-2 is constitutively expressed in neurons. Animal expts. suggest that COX-2 may be performing adaptive functions assocd. with normal neurons and protective functions assocd. with stressed neurons. These results emphasize that the appropriate target for NSAID trials in AD is COX-1, but they also indicate that there would be no contraindication to the use of those traditional NSAIDs which have mixed COX-1/**COX-2 inhibiting** activity.
REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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ACCESSION NUMBER: 2000:251152 HCAPLUS
DOCUMENT NUMBER: 133:12237
TITLE: Anti-inflammatory drugs: a hope for Alzheimer's disease?
AUTHOR(S): Hull, Michael; Lieb, Klaus; Fiebich, Bernd L.
CORPORATE SOURCE: Department of Psychiatry and Psychotherapy, University of Freiburg Medical School, Freiburg, D-79104, Germany
SOURCE: Expert Opinion on Investigational Drugs (2000), 9(4), 671-683
CODEN: EOIDER; ISSN: 1354-3784
PUBLISHER: Ashley Publications
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 123 refs. Human brain cells are capable of initiating and amplifying a brain specific inflammatory response involving the synthesis of cytokines, acute-phase proteins, complement proteins, prostaglandins and oxygen radicals. In Alzheimer's disease (AD), all signs of an inflammatory microglial and astroglial activation are present inside and outside amyloid depositions and along axons of neurons with neurofibrillary tangles. Cell culture and animal models suggest a bidirectional relationship between inflammatory activation of glial cells and the deposition of amyloid. Although it remains unclear which of the different pathophysiol. processes in AD may be the driving force in an individual case, the inflammatory activation may increase the speed of cognitive decline. Epidemiol. studies point to a reduced risk of AD among users of anti-inflammatory drugs. Therefore, anti-inflammatory drugs have become the focus of several new treatment strategies. A clin. trial with the non-steroidal anti-inflammatory drug (NSAID) indomethacin showed promising results, while a clin. trial with steroids did not show a beneficial effect. Further trials with NSAIDs such as unselective cyclooxygenase (COX) and selective cyclooxygenase-2 (**COX-2**) **inhibitors** are on their way. COX inhibitors may not only act on microglial and astroglial cells but also reduce neuronal prostaglandin prodn. New data suggest that prostaglandins enhance neurotoxicity or induce pro-inflammatory cytokine synthesis in astroglial cells. Amongst these promising new strategies to reduce microglial or monocyte activation, interfering with intracellular pathways has been shown to be effective in various cell culture and animal models but clin. studies have not yet been performed.

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ACCESSION NUMBER: 2000:147372 HCAPLUS
DOCUMENT NUMBER: 132:273659
TITLE: New anti-inflammatory treatment strategy in Alzheimer's disease
AUTHOR(S): Sugaya, Kiminobu; Uz, Tolga; Kumar, Vinod; Manev, Hari
CORPORATE SOURCE: The Psychiatric Institute, West Side VA Medical Center, Department of Psychiatry, University of Illinois at Chicago, Chicago, IL, 60612, USA
SOURCE: Japanese Journal of Pharmacology (2000), 82(2), 85-94
CODEN: JJPAAZ; ISSN: 0021-5198
PUBLISHER: Japanese Pharmacological Society

DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 111 refs. Numerous reports have indicated that patients suffering from inflammatory diseases (e.g., arthritis) who take anti-inflammatory medication have a reduced risk of developing Alzheimer's disease (AD). Thus, the first generation of anti-inflammatory cyclooxygenase (COX) inhibitors, such as aspirin and indomethacin, have been tested as potential therapeutics in AD. Because the inhibition of COX-1 is also known to cause tissue damage in the gastrointestinal system from the resultant reduced cytoprotection, selective **COX-2 inhibitors** are being investigated and tested clin. as potentially better therapeutics for AD patients. However, such drugs may also trigger unwanted effects; for example, the **COX-2 inhibitors**, which reduce the prodn. of one type of eicosanoids, the prostaglandins, may increase the prodn. of other eicosanoids; i.e., the leukotriene B4 (LTB4), which is one of the most potent endogenous chemotactic/inflammatory factors. LTB4 prodn. is initiated by the enzyme 5-lipoxygenase (5-LOX). The expression of the 5-LOX gene is upregulated during neurodegeneration and with aging. In spite of the fact that 5-LOX and leukotrienes are major players in the inflammation cascade, their role in AD pathobiol./therapy has not been extensively investigated. We propose that the 5-LOX inflammatory cascade may take part in the process of aging-assocd. neurodegenerative diseases, and we point to the role of 5-LOX in neurodegeneration and discuss its relevance for anti-inflammatory therapy of AD.
REFERENCE COUNT: 111 THERE ARE 111 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L100 ANSWER 11 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
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ACCESSION NUMBER: 1999:397414 HCAPLUS
DOCUMENT NUMBER: 131:67542
TITLE: The clinical potential of cyclooxygenase-2-specific inhibitors
AUTHOR(S): Lipsky, Peter E.
CORPORATE SOURCE: Rheumatic Diseases Division, Harold C. Simmons Arthritis Research Center, The University of Texas Southwestern Medical Center at Dallas, Dallas, TX, 75235, USA
SOURCE: American Journal of Medicine (1999), 106(5B), 51S-57S
CODEN: AJMEAZ; ISSN: 0002-9343
PUBLISHER: Excerpta Medica, Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 51 refs. Emerging evidence suggests that cyclooxygenase-2 (COX-2) has diverse physiol. and pathophysiol. functions. It is expressed constitutively in the developing kidney and brain, playing a role in their proper maturation and function. Further, COX-2 expression may be up-regulated at certain sites: in the kidney during sodium restriction; in the microglia of cognitive centers within the hippocampus and cortex in Alzheimer's disease; and in intestinal adenomas and colon tumors. On the basis of COX-2 expression in Alzheimer's disease and colon cancer, COX-2-specific inhibitors may find clin. utility in the prevention or treatment of these conditions. Despite this apparently optimistic outlook for future uses of **COX-2 inhibitors**, most of the findings supporting this perspective are based on in vitro and in vivo models and must be rigorously corroborated in human studies, some of which are already planned.
REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS